DOES NOT CIRCULATE

—Symposium on Arteriosclerosis—

UNIVERSITY OF MICHIGAN
JAN 10 1956
MEDICAL LIBRARY

Minnesota MEDICINE

PUBLISHED MONTHLY BY THE MINNESOTA STATE MEDICAL ASSOCIATION

Volume 38 NOVEMBER, 1955 Number 11

Printed in U.S.A.

(Table of Contents—Pages ii and iii)

40c a copy—$3.00 a year

Tonsillitis, pharyngitis quickly yield to

ILOTYCIN

(Erythromycin, Lilly)

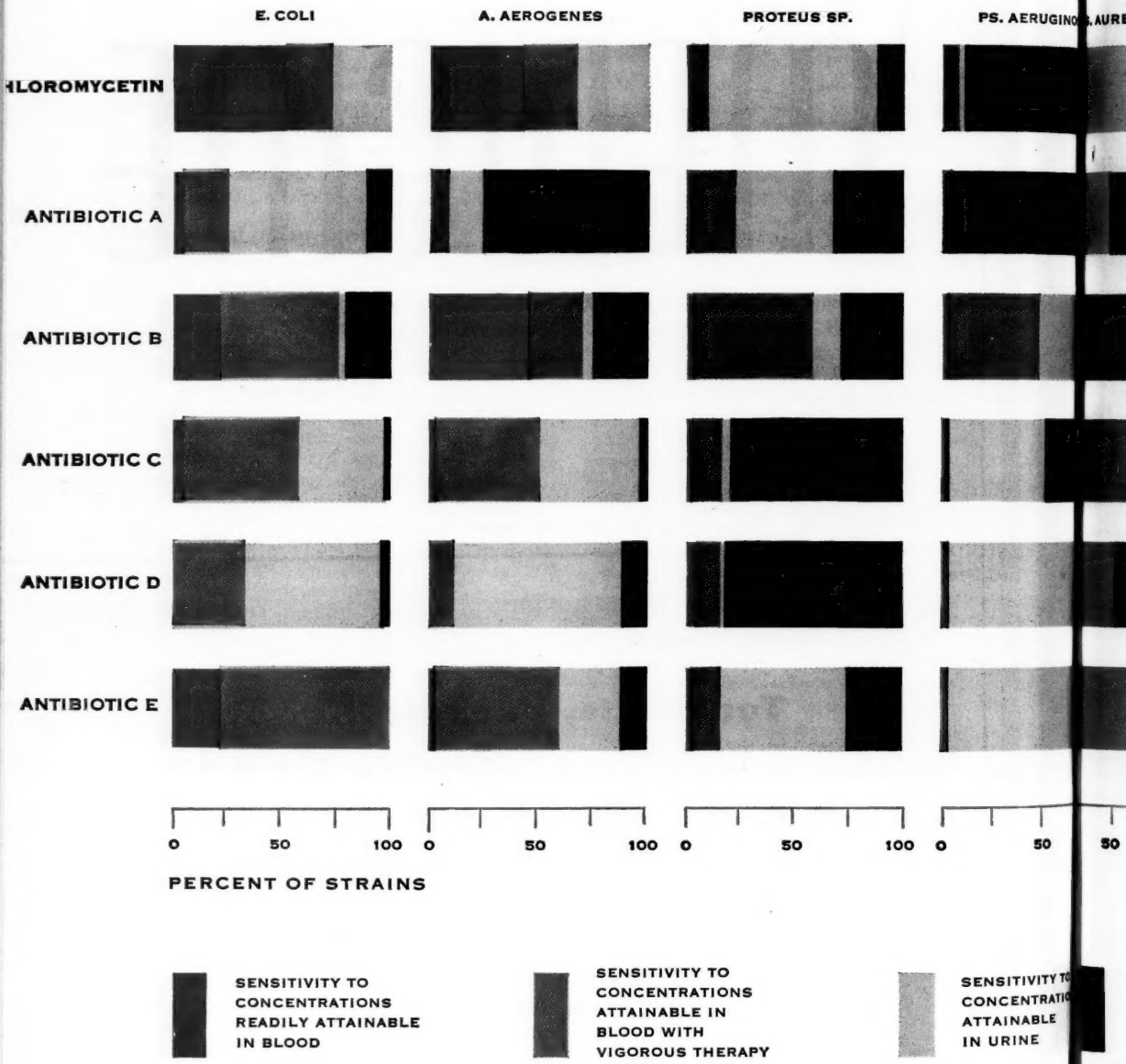
Temperature rapidly returns to normal; swelling and soreness readily subside. Notably safe and well tolerated.

dosage: Usually, 250 mg. q. 6 h. Children, 5 mg. per pound of body weight q. 6 h.

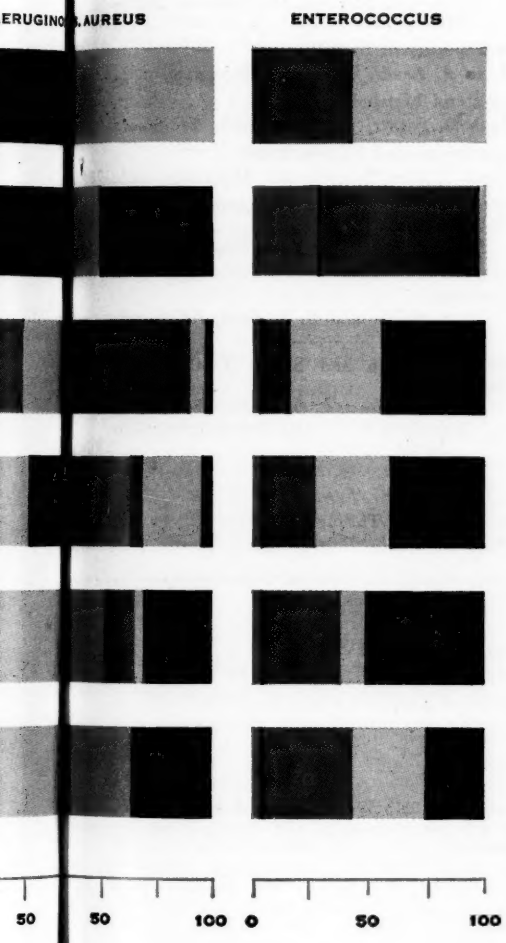
Lilly

532200

esistance of Common Urinary Tract Pathogens to CHLOROMYCETIN and Other Major Antibiotic



less resistance encountered...



Adapted from Kass, E. H.

Chloromycetin

for today's problem pathogens

Recent in vitro tests and clinical studies again demonstrate the unsurpassed efficacy of CHLOROMYCETIN (chloramphenicol, Parke-Davis) against a wide variety of pathogens. For example, against urinary infections, now characterized by increased incidence of resistant gram-positive and gram-negative strains, CHLOROMYCETIN continues to provide outstanding antibacterial action.[1-11]

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

References (1) Altemeier, W. A.; Culbertson, W. R.; Sherman, R.; Cole, W.; Elstun, W., & Fultz, C. T.: *J.A.M.A.* 157:305, 1955. (2) Kutscher, A. H.; Seguin, L.; Lewis, S.; Piro, J. D.; Zegarelli, E. V.; Rankow, R., & Segall, R.: *Antibiotics & Chemother.* 4:1023, 1954. (3) Clapper, W. E.; Wood, D. C., & Burdette, R. I.: *Antibiotics & Chemother.* 4:978, 1954. (4) Sanford, J. P.; Favour, C. B.; Harrison, J. H., & Mao, F. H.: *New England J. Med.* 251:810, 1954. (5) Balch, H. H.: *Mil. Surgeon* 115:419, 1954. (6) Sanford, J. P.; Favour, C. B., & Mao, F. H.: *J. Lab. & Clin. Med.* 45:540, 1955. (7) Felshin, G.: *J. Am. M. Women's A.* 10:51, 1955. (8) Jones, C. P.; Carter, B.; Thomas, W. L., & Creadick, R. N.: *Obst. & Gynec.* 5:365, 1955. (9) Kass, E. H.: *Am. J. Med.* 18:764, 1955. (10) Stein, M. H., & Gechman, E.: *New England J. Med.* 252:906, 1955. (11) Yow, E. M.: *Postgrad. Med.* 17:413, 1955.

MEDICAMENTA VERA

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

Volume 38

Minnesota M

Contents for Ma

SCIENTIFIC ARTICLES

SYMPOSIUM ON ARTERIOCLEROSIS

The Challenge of Arteriosclerosis

Challenge of Arteriosclerosis to Medical Education
William F. Maloney, Minneapolis, Minnesota 731

Role of the National Heart Institute in Meeting the Challenge of Arteriosclerosis
James Watt, Bethesda, Maryland..... 734

Life Insurance Looks at the Arteriosclerosis Problem
William P. Shepard and *Herbert H. Marks,* New York, New York..... 736

Strategy and Tactics of Research in Arteriosclerosis
Irvine H. Page, Cleveland, Ohio..... 743

Pleomorphism of the Lesions of Arteriosclerosis
G. C. McMillan, Montreal, Quebec..... 746

Factors Other than Cholesterol in Arteriosclerosis
William B. Wartman, Chicago, Illinois..... 749

Atherosclerosis

The Atherosclerosis Problem
Louis N. Katz, Chicago, Illinois..... 755

Mode of Life and the Prevalence of Coronary Heart Disease
Ancel Keys, Minneapolis, Minnesota..... 758

Lipoprotein Metabolism in the Etiology of Atherosclerosis
Christian B. Anfinsen, Jr., Bethesda, Maryland 767

The Lipoprotein System
Lena A. Lewis, Cleveland, Ohio..... 775

Cholesterol Metabolism
Ivan D. Frantz, Jr., Minneapolis, Minnesota 779

Hypertension and Atherosclerosis
Louis Tobian, Minneapolis, Minnesota..... 784

Hormonal Factors in the Pathogenesis of Atherosclerosis
David P. Barr, New York, New York..... 788

Coronary Atherogenesis—An Endocrine Problem?
M. F. Oliver and *G. S. Boyd,* Edinburgh, Scotland 794

Urinary Estrogen and Serum Protein-bound Iodine Levels
Jessie Marmorston, Olive Hoffman, Harry Sobel and *Paul Starr,* Los Angeles, California 800

The Coronaries

The Coronaries Through the Ages
Paul D. White, Boston, Massachusetts..... 801

Official Journal of

Duluth Surgical Society
Minneapolis Academy of Medicine
Minneapolis Surgical Society
Minnesota Academy of Medicine
Minnesota Society of Clinical Pathologists

Owner and Publisher

Published by MINNESOTA STATE MEDICAL ASSOCIATION
496 Lowry Medical Arts Building
St. Paul 2, Minnesota

Editing and Publishing Committee

E. M. HAMMES, M.D.
Chairman, Saint Paul

F. M. OWENS, JR., M.D.
Saint Paul

T. A. PEPPARD, M.D.
Minneapolis

HENRY ULRICH, M.D.
Minneapolis

Business Manager

R. R. ROSELL
496 Lowry Medical Arts Building
St. Paul 2, Minnesota

GENERA

Authors

Manuscripts should be addressed to Arthur H. Wells, M.D., Editor, 915 East Fir Street, Duluth 5, Minnesota. Telephone RA 7-6636 or JA 5-2319. Original papers prepare for publication solely in MINNESOTA MEDICINE will be considered by the Board of Editor providing they fulfill the following editorial standards. Manuscripts should be type double spaced on white paper with at least 1-inch margins. The original (not a carbo copy) is requested. The title on the first page should be under six words if possibl or divided into two parts. The author should give his highest degree, his institutiona position or his relationship to a hospital or medical organization which he may b addressing. Pages should be numbered consecutively and the author's last name should appear at the top of each page after the first page.

Biographical references should appear on a separate sheet entitled "Bibliography." They should appear and be numbered consecutively in the order in which they first occur in the text (not alphabetically). Citations in the text require reference numbers if the author's or authors' names are not used or if there is more than one reference to the same author or group of authors. All references to author should appear in the Bibliography and no references should be included which are not in the text. The style and exact punctuation used in the J.A.M.A. references is requested. For a journal this is: *Author's last name, initial, initial.: title of paper. Abbreviated name of journal, volume number: page, year.* Book references should give author, title, edition number, city, publisher and year.

Illustrations (photographs, tables and graphs) should be submitted separately and not combined in the text. There should be a separate sheet entitled "Illustrations" which contains the various types of illustrations listed separately and numbered in the order

Medicine

Number 11

for November, 1955

MISCELLANEOUS ARTICLES

CASE PRESENTATION

Diabetes Insipidus and Pregnancy
Charles H. McKenzie, M.D., and *Francis M. Swain, M.D.*, Minneapolis, Minnesota 809

LABORATORY AIDS

Exfoliative Cytology: A Realistic Appraisal
John R. McDonald, M.D., Rochester, Minnesota 812

EDITORIALS

Physical Medicine 814
Psychiatric Consultation in Social Agencies 814
Separate Fund-raising 815
Design and Decoration for the Doctor's Office 816
Ancilla,-ae, *f.dim* 817

IN MEMORIAM

Jack Friedman 817

PRESIDENT'S LETTER

Something Good 818

MEDICAL ECONOMICS

Survey Shows Public Likes M.D.'s 819
AMA Studies Medical Care Economics 820
America Called Medical Magnet 821

THE DEAN'S PAGE

The Fall Semester Begins 822

LETTERS 823

REPORTS AND ANNOUNCEMENTS 826

GENERAL INTEREST

Personal News 827
New Locations xli
Minnesota Blue Shield-Blue Cross xli

BOOK REVIEWS xliii

ABSTRACTS li

CLASSIFIED ADVERTISING lvi

INDEX TO ADVERTISERS lvii

Minnesota Society of Internal Medicine
Minnesota State Medical Association
Minnesota Obstetric and Gynecologic Society
Minnesota Surgical Society
Northern Minnesota Medical Association
Southern Minnesota Medical Association

INFORMATION

in which they appear in the text. All photographs must be in black and white, clear cut, contrasting, and on glossy prints. Instructions for combining photographs are acceptable. Any number of illustrations over 4 are charged to the author. Combinations of photographs up to one-half page (6 x 4⅜ inches) count as 1 illustration.

Readers and Reviewers

The right is reserved to reject material submitted for reading or advertising columns. The views expressed in this journal do not necessarily represent those of the Minnesota State Medical Association or any of its constituents.

Advertisers and Subscribers

Classified advertising—10 cents a word; minimum charge $2.00; key number, 25c additional. Remittance should accompany order. Display advertising rates on request. Telephone Midway 6-2641.

Annual Subscription—$3.00. Single Copies—$0.40. Foreign and Canadian—$3.50.

Communications concerning advertising and subscriptions should be addressed to MINNESOTA MEDICINE, 2642 University Avenue, Saint Paul 14, Minnesota.

Copyright and Post Office Entry

Contents of MINNESOTA MEDICINE ©1955 by Minnesota State Medical Association.

Entered at the Post Office in Saint Paul as second class matter. Accepted for mailing at the special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 13, 1918.

Board of Editors

ARTHUR H. WELLS, M.D.
Editor-in-Chief, Duluth

STUART W. ARHELGER, M.D.
Minneapolis

JOHN F. BRIGGS, M.D.
Saint Paul

ALEX E. BROWN, M.D.
Rochester

S. FRANCIS CEPLECHA, M.D.
Redwood Falls

TAGUE C. CHISHOLM, M.D.
Minneapolis

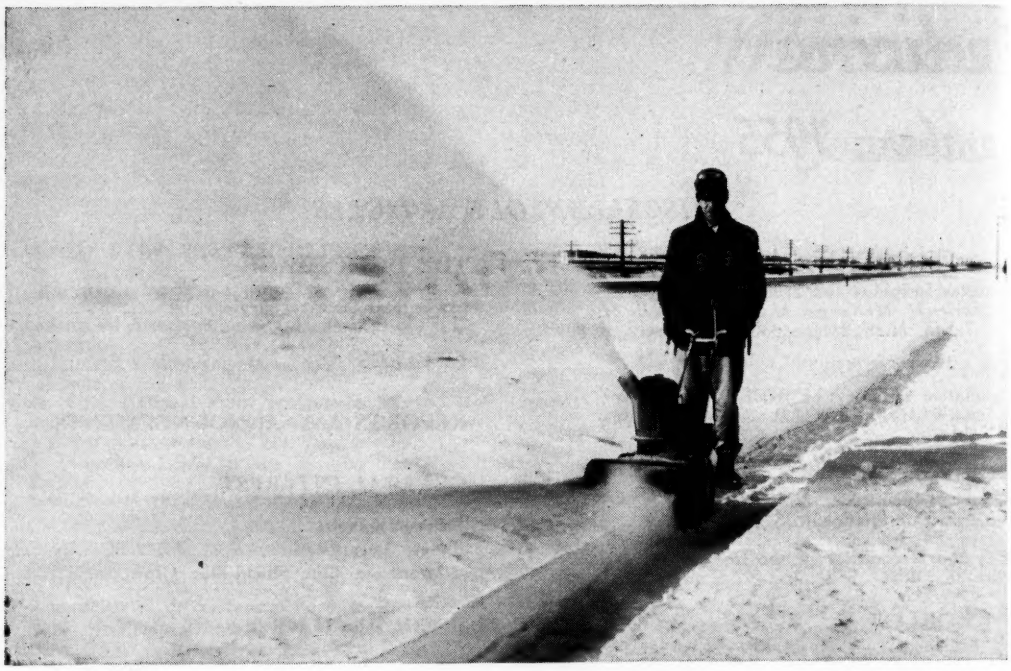
ROBERT B. HOWARD, M.D.
Minneapolis

HENRY G. MORRING, M.D.
Duluth

GLENN J. MOURITSEN, M.D.
Fergus Falls

OLIVE V. SEIBERT, B.A.
Saint Paul

GEORGE STILWELL, M.D.
Rochester



Why you need 3½ HP to plow snow

Because Plow Does ALL The Work; You Only Steer It

Here's a sidewalk rotary snow plow that won't mulch leaves, mow grass or dig gardens, but it *will* plow snow from here to breakfast for you.

The *Sno-Flyr's* 3½ HP engine makes an effortless task out of the lung bursting job of clearing sidewalks and driveways; it does *all* the work — you just guide it.

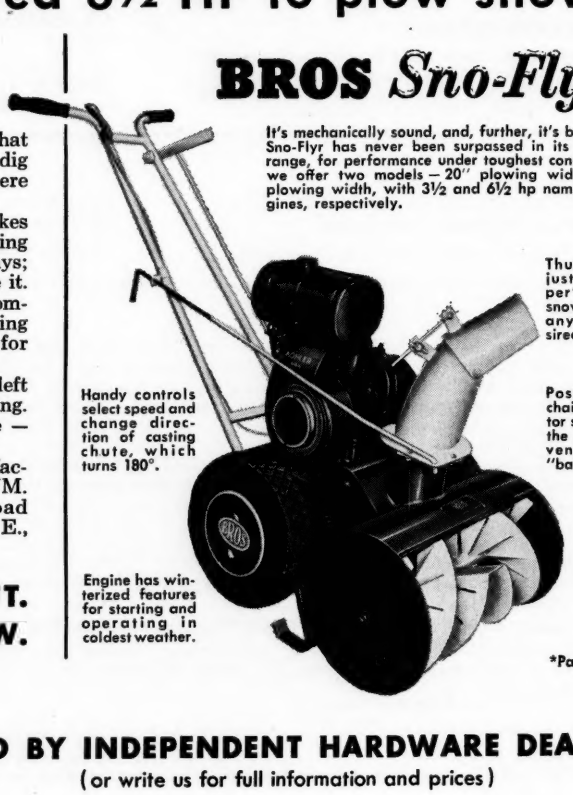
Engine has two speeds: *slow* (comparable to low gear driving) for plowing heavy, wet or deep snow; and *normal* for light snow plowing at walking speed.

Casting chute revolves in arc from left to right for full control of snow casting. It throws 600 lbs. of snow per minute — up to 25 feet in distance.

Made by the world's largest manufacturer of rotary snow plows, THE WM. BROS BOILER & MFG. CO., Road Machinery Div., 1057 Tenth Ave. S. E., Minneapolis 14, Minnesota.

DON'T WAIT FOR 2 FT. OF SNOW: ORDER NOW.

BROS *Sno-Flyr**


It's mechanically sound, and, further, it's bug-free. The Sno-Flyr has never been surpassed in its horsepower range, for performance under toughest conditions. And we offer two models — 20" plowing width and 26" plowing width, with 3½ and 6½ hp name brand engines, respectively.
Thumb-nut adjustable "capper" deflects snow stream to any height desired.
Handy controls select speed and change direction of casting chute, which turns 180°.
Positive roller chain drive. Rotor slots "knife" the snow, preventing rotor "balling."
Engine has winterized features for starting and operating in coldest weather.
BROS

*Pat. Pending

BROS

SOLD BY INDEPENDENT HARDWARE DEALERS

(or write us for full information and prices)

The Challenge of Arteriosclerosis

Challenge of Arteriosclerosis to Medical Education

WILLIAM F. MALONEY
Minneapolis, Minnesota

WHEN first assigned this title, my reaction was one of amazement. Did the program committee really think that our medical schools are afflicted with arteriosclerosis? Did they really want me to deliver a tirade about the hardening of the arteries of our educational system? This did not seem appropriate, nor did it seem that a degenerative process had begun its inexorable progress in the body of our medical educational system. I recognized, of course, (as we all do) that only by keeping curriculi flexible and adaptable, and by keeping faculty minds open to new educational methods and ideas in this swiftly changing era of medicine, can our schools fulfill their obligation to society; that only by conscientious effort to remain aware not only of the changes in medical knowledge, but also aware of the changing place of medicine and the physician in our society can the schools prepare doctors who will adequately carry out the task of ever-raising the health level of our people. Inelasticity and occlusion are not unknown in medical education, but this is a relatively rare occurrence, as distinguished from its incidence in the population.

But since arteriosclerosis is the subject of this symposium, I ruminated a bit about our medical educational system in terms of just how adequate, adaptable and dynamic it had been in dealing with this subject matter. It was soon apparent that the subject matter of the condition arteriosclerosis itself presented a tremendous challenge to teaching. It was also apparent that medical education had met this challenge well to date. And finally, it was apparent that the most appropriate discussion for today was one that centered around the challenge arteriosclerosis represented in terms of producing physicians who were knowledgeable about this subject.

Immediately obvious, is the fact the arteriosclerosis occupies many times more pages in the 1955 editions of leading textbooks of medicine than in the 1925, and that curriculum time devoted to this material has increased in several instances from as little as zero to a significant percentage during a comparable period. It is apparent also that the study of this entity now cuts across virtually all departmental lines—both basic science and clinical.

For purposes of discussion, let me propose one description of arteriosclerosis. It may be described as a condition of unclear etiology, involving fundamental physiological and anatomical alterations that are influenced by physical, chemical, genetic, environmental and psychological factors. A high incidence, a wide variety of clinical manifestations, and prolonged disability are characteristic. Arteriosclerosis as thus described is at every point a challenge to medical education.

The reforms in medical schools and medical education, stimulated by the Flexner Report in 1910, ushered in what has come to be known as "scientific" medicine. Biology, chemistry and physics have come to occupy central positions in medical teaching. Dr. Donald Anderson, the

From the University of Minnesota Medical School.
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

former secretary of the Council on Medical Education, has considered "the thoroughness with which we have sought to apply the facts and techniques of the basic sciences to clinical medicine" as being "the outstanding feature of medical education in this era." In his words, "The transformation of clinical medicine into a real science, and conversion (at least partially successful) of the physician from an empiricist to a scientist who daily applies scientific methods and the techniques of the laboratory to the problems presented by his patients, is a development to which must be credited most of the gains in medical education in the past half century."[1]

The emphasis on basic experimental science in the pre-clinical years of medical education continues to be appropriate, particularly with regard to the subject matter of this symposium. The elucidation of the fundamental alterations in the physiological processes, and of the etiology of the anatomical alterations known to occur with arteriosclerosis can continue to be accomplished only by individuals thoroughly familiar with basic principles and techniques in the natural sciences, and with the ability to use this knowledge critically and with originality.

However, as defined by the Association of American Medical Colleges, it "should not be the aim of undergraduate medical education to present the complete, detailed, systematic body of knowledge concerning each and every medical and related discipline." Rather, emphasis must be placed on "learning fundamental principles applicable to the whole body of medical knowledge; of establishing habits of reasoned and critical judgment of evidence and experience; and developing an ability to use these principles and judgments wisely in solving problems of health and disease."[2]

Thus, the continued emphasis on basic science is important, but the emphasis on major principles is not only more productive in preparing young minds for original thinking, but also has been made absolutely essential by the continuing rapid accumulation of scientific fact and detail which threatens to overwhelm the educational enterprise.

Factual basic science knowledge is accumulating rapidly in the field of arteriosclerosis. This raises an even more fundamental problem. Just which "facts" does one teach? No educator that I know of has an entirely satisfactory solution to this quandary. There is, however, educational value in the very quandary itself. It serves brilliantly to assist in making students critical of experimental evidence, healthily skeptical of "facts," cautious in their judgment, and respectful of the magnitude of the problems to be solved.

Yet another facet of this problem must be dealt with. The accumulating evidence that hereditary factors, psychological elements, living habits and social forces may affect this process so increases the scope of the orientation necessary as to challenge the limits of a four year curriculum. Here again, undergraduate medical education does not and cannot attempt to provide a detailed presentation of all these factors in addition to the physical, chemical and biological agents and alterations that may affect the human being.

However, the recognition of the relevance of these other factors, in addition to the basic disciplines of "scientific" medicine, has brought to medical education a new period of development called by some "comprehensive" medicine. George Packer Berry, dean of the Harvard Medical School, expresses it in this manner:

> "The trend today is toward an internal synthesis of the scientific facts about man, and an expansion of our view to embrace what for simplicity can be described as the psychological and sociological facets of the patient. It is not so much that these aspects of the patient have been ignored in the past—they have been inherent in the doctor's appraisal of the patient since the time of Hippocrates—but the newer disciplines of psychiatry and social anthropology and allied fields now provide us with a great deal more insight into the nature of disease, into man's relationship with man, and the factors that make for healthy community life. To equip our doctors in training to meet the new challenge . . . we must broaden the base of our training, expanding the concept of scientific medicine to that of comprehensive medicine, where all the benefits that have accrued . . . will be retained with the addition of new studies of the patient in his socio-psycho setting."[3]

Degenerative vascular disease contributes a major and ever-increasing percentage of the problems with which comprehensive medicine concerns itself. The development in the student of a suitable orientation toward these problems, without interfering with a sound training in medicine as it has been developed on the basis of the natural sciences, is a difficult problem.

An increasing amount of experimentation has been taking place in medical education in recent years, in an effort to deal with this problem. Dr. Herman Weiskotten summarized this in a paper read at the Annual Congress on Medical Education two years ago. I quote him:

"Frequently such new subject matter has not appeared to fit readily into the program of existing departments. Attempts have been made to present it to the students in didactic form, as separate courses detached and isolated from the pre-existing curriculum content. Such attempts have not been too successful, and the schools have been faced with the problems of attempting to incorporate such new subject material into the individual experiences of the student in the integrated programs of the basic medical science and clinical departments.

"Here again, the solutions of these problems have required not only continued re-evaluation of the course content of the various departments, but also continued experimentation as to how in a given school important new subject matter and viewpoints can be best integrated into the basic training of the student.

"Just as individual faculty members are continually conducting research for the advancement of medical science in their particular fields, as faculty groups they should continually be conducting experiments in the field of medical education—for this is the primary responsibility of our Medical schools and must always be recognized as such."[4]

A natural outcome of the concept of comprehensive medicine has been a broader interpretation of medicine's role in the community. The possibility of control of some of the factors responsible for arteriosclerosis as our increased understanding suggests, has caused the science of preventive medicine to assume new and greater importance.

Another addition to the medical educational program has been the teaching of the science and art of rehabilitation. The prolonged disability which most commonly results from the occurrence of arteriosclerosis in several of its forms presents a challenging problem. It has been clearly demonstrated that rehabilitation has much to offer in this field.

Again, the objectives of medical education, as enunciated by the Association of American Medical Colleges, carry beyond teaching diagnosis and treatment to "helping the student to achieve basic skills in working in the medical team of physician, nurses, social workers, physical therapists and others; and in working in the community team of official and voluntary institutions and agencies providing health services; as well as that of helping the student to develop sound attitudes for basing the plan for cure, rehabilitation or adjustment to permanent handicap upon the joint efforts of the medical team and the patient."[2]

Not all educators have broadened their horizons to understand or teach in terms of comprehensive medicine. However, arteriosclerosis in its implications for the health of the total community will eventually be a principal force in compelling them to greater perspective. On the other hand, I submit that this nation's medical schools, in carrying out their functions of teaching, research and service, have for the most part accepted challenges so well that they have given themselves the greatest challenge of all—an ever-increasing prevalence of degenerative vascular disease as a result of the ever-lengthening life span. As our own professor emeritus of pathology, Doctor Bell, once remarked, "The only thing left to die of will be arteriosclerosis." This challenge should be enough to keep the arteries of medical education elastic and patent.

References

1. Anderson, Donald G.: Medical education; a look ahead. J.A.M.A., 145:478-480 (Feb. 17) 1951.
2. Association of American Medical Colleges: The objectives of undergraduate medical education. J. Med. Education, 28:57-59 (March) 1953.
3. Berry, George Packer: Committee Report, First Teaching Institute of the Association of American Medical Colleges (Oct.) 1953.
4. Weiskotten, H. G.: Experimentation in medical education. J.A.M.A., 151:1486-1488 (April 25) 1953.

A chronic disease or condition may be defined as one which lasts a long time or at least too long and which, while it is present, prevents the individual from operating at his optimum efficiency. The cause may be a disease, as in the case of poliomyelitis, tuberculosis or syphilis of the central nervous system. It may be a physical or mental injury or dysfunction as in the case of cerebral palsy, an accidental amputation, mental retardation, or excessive exposure to radiation.—DANIEL BERGSMA, M.D., *New Jersey Pub. Health News*, April, 1955.

Role of the National Heart Institute in Meeting the Challenge of Arteriosclerosis

JAMES WATT
Bethesda, Maryland

IN August, 1948, the Congress of the United States enacted legislation creating the National Heart Institute, a division of the National Institutes of Health, Public Health Service. As part of this legislation, the Congress specifically charged the National Heart Institute with the responsibility of improving the health of the people of the United States as related to disorders of the heart and circulation. The National Heart Institute was authorized to do this through the carrying on of research, by assisting and fostering research and other activities by public and private agencies, by providing training for research workers and clinicians, and by assisting the states and other agencies in the use of the most effective methods of prevention, diagnosis, and treatment of diseases of the heart and circulation.

In carrying out these responsibilities, the National Heart Institute has utilized several programs. Today, I would like to review for you some of the accomplishments, some of the frustrations, and some of the dreams that these approaches have nurtured in one area of cardiovascular disease—arteriosclerosis.

The largest of these programs, in terms of man-hours and dollars expended over the past six years, has concerned itself with the encouragement and support of research. The awarding of research grants to universities, hospitals, and laboratories throughout the country and the carrying on of research in the laboratories of the National Heart Institute at Bethesda, Baltimore, and Framingham are the main facets of the National Heart Institute research program.

Upon recommendation of the National Advisory Heart Council, the Surgeon General has awarded, since 1948, approximately 4.5 million dollars in grants for the support of research related to arteriosclerosis to laboratories other than those of the Public Health Service. These awards have provided funds for the organization and operation of new laboratories, for the stimulation of increased effort in already established laboratories, and for the encouragement of introducing new views and new skills to the basic and applied problems related to arteriosclerosis.

The results of these efforts are well documented in scientific and medical journals. A major step forward is the realization and demonstration that arteriosclerosis, particulary atherosclerosis, is not an inevitable part of aging, but rather a pathologic process afflicting some people at a relatively early age, others practically not at all. To study this pathologic process, techniques have been developed to produce atherosclerotic lesions in a variety of experimental animals. The utilization of these animals has permitted the establishment of controlled studies in which some of the variables associated with this disease can be studied separately. The artery wall has been introduced as an active factor in the production of the lesion; the role of the cellular and non-cellular elements circulating in the blood — phagocytes, cholesterol, phospholipids, lipoproteins, and neutral fats—are being studied; the physical forces—hypertension, blood eddying, friction, adsorption, and surface tension—are being looked at and evaluated in terms of this problem; the role of the liver, of the endocrine glands, of the gastrointestinal tract is being scrutinized. Some of the newer research techniques as used in biophysics, in ultamicroscopy, and in enzyme chemistry have yet to be extensively applied to the area of arteriosclerosis; the same can be said of some of the older established techniques, those of the geneticist, the epidemiologist, and the environmental engineer.

From the National Heart Institute, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland.
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

In the laboratory of the clinical scientist, new methods of diagnosis and treatment are under surveillance. As yet, excluding histological study after biopsy, we regretfully realize that the only generally accepted method of diagnosis depends upon the onset of clinical symptoms or signs. The search for reliable tools or methods for preclinical diagnosis is being pursued, and we hope the results of these efforts will be available to the clinician before long. In the area of therapy, exciting surgical techniques for the repair of blood vessels have been reported. The artery bank is now a reality; the use of prosthetics for the replacement of injured blood vessels is no longer a dream. There have been many disappointments in drug and hormonal therapy for the prevention or treatment of atherosclerosis, but with each failure a glimmer of a new possibility arises. Techniques for the rehabilitation of those afflicted with this disease are slowly being developed.

As part of the research effort directed against arteriosclerosis, scientists working in the laboratories of the National Heart Institute are pursuing similar problems. A coordinated plan of investigation already under way at Bethesda has been greatly accelerated by the establishment of the Clinical Center. Here, preclinical and clinical scientists are able to integrate their activity in specially selected patients for periods of time considerably longer than those usually available to workers in the average hospital situation. Having animal and patient laboratories in close approximation has permitted parallel controlled investigations to be initiated. As yet, many of our laboratories are just now being completed, equipped, and staffed, but in those already in operation the mechanisms of lipid transport and metabolism are being studied. The relationship of proteins, heparin, clearing factor and certain drugs and hormones to the development of atherosclerosis has commanded our interest.

Many of you are aware of the heart disease epidemiology study being conducted at Framingham, Massachusetts. There, in cooperation with local physicians and community health agencies, the genetic and environmental factors believed to be significant in the development or progression of arteriosclerosis and hypertension are being investigated. About two-thirds of the adults in this community between the ages of thirty and fifty-nine, including several thousand volunteer participants selected by random sampling methods, are part of the study. These persons will be followed over an extended period, during which data of pertinent constitutional or conditioning factors will be recorded and analyzed.

These examples reflect a few of the ways in which the research grant and direct research programs of the Institute are assisting in the development of new knowledge about arteriosclerosis.

Another area of considerable interest to the National Heart Institute has been the need for additional research workers and clinicians leading to the establishment of its research fellowship and clinical traineeship programs. These training programs at the predoctoral and postdoctoral levels aid young men and women in obtaining training in laboratories and clinics concerned with arteriosclerosis. During this training period, a living stipend, tuition, and travel funds are made available. For the more experienced man, a special fellowship or traineeship can be provided. These awards permit the trainee to assimilate new techniques and obtain instruction in the disciplinary background needed to search out and investigate meaningful problems or to more skillfully utilize the tools of clinical medicine for better patient care.

Recognizing also the need for other training programs for scientists and clinicians, the Institute supports an undergraduate and graduate training grant program. Through this program, funds are made available to universities, hospitals, and laboratories for the establishment, expansion, or improvement of instruction in areas related to arteriosclerosis or other cardiovascular matters. These funds have been used for the support of trainees, of staff, and for the provision of the facilities needed to maintain these programs of instruction.

Thus, by means of the research fellowship, the traineeship, and the training grant programs, we hope to maintain and encourage an increase in the pool of highly skilled research workers and clinicians. We at the National Heart Institute consider these training programs essential, for we realize that the answers to the problem of arteriosclerosis and their application to the

(Continued on Page 742)

Life Insurance Looks at the Arteriosclerosis Problem

WILLIAM P. SHEPARD and
HERBERT H. MARKS
New York, New York

THE awareness and the concern of the life insurance industry over the problem of arteriosclerosis is perhaps best indicated by the Life Insurance Medical Research Fund organized ten years ago. Although the purpose of the fund is to support medical research in any field, its resources have been devoted to research bearing on diseases of the heart and arteries and fundamental related problems. In addition to supporting research, the fund also fosters the development and training of research personnel of high calibre by financing graduate fellowships. Over 140 life insurance companies, which account for 90 per cent of the life insurance in force in the United States, now contribute to the fund, which to date has appropriated more than $7,200,000 for its work. The companies are now contributing nearly $1,000,000 annually. While these sums may seem small in relation to the volume of business and resources of insurance companies, it must be remembered that the life insurance business is rigidly supervised and subject to strict laws with regard to expense limits. To date, 247 research programs have been supported by grants and 302 fellowships have been given to young men and women to enable them to obtain research training in the field of cardiovascular disease. Research has thus been aided in 110 institutions, most of them in the United States and Canada.[1,2]

Since I have been asked to talk on the problem of arteriosclerosis as seen from the point of view of life insurance, I have purposely picked out for my discussion certain aspects on which information available from life insurance records is particularly useful. These are (1) the extent of the problem in terms of mortality and morbidity, (2) the trends in mortality, (3) facts relating to prevention and control, and (4) facts relating to prognosis.

The facts I present will, of necessity, relate generally to aggregates such as cardiovascular-renal diseases or heart disease because conditions due to or associated with arteriosclerosis are not combined in a separate aggregate in the statistics on mortality and morbidity. Arteriosclerosis is, however, the predominant etiological factor in the categories covered in my material.

It is no secret that a major reason for the concern of the companies is that from the standpoint of claims, disorders associated with or due to arteriosclerosis constitute a large and increasing proportion of the total. This holds not only for death claims, but to an increasing extent for temporary and permanent disability and hospitalization.

Mortality from "Arteriosclerosis"

More than two billion dollars in death claims were paid to American families by life insurance companies during 1954.[3] While we do not know exactly the amount of money paid out for the various causes of death, cardiovascular-renal disease in 1954 accounted for well over half of the deaths among insured persons from all causes, and for 60 per cent or more of the deaths from disease. The major proportion of these deaths reflects the toll from arteriosclerosis. In addition, the condition is a factor in deaths from diabetes and certain other causes, especially in older persons.

Figures on deaths in 1952 among persons insured under *ordinary* policies, presented in Figure 1, show that cardiovascular-renal diseases accounted for 57 per cent of the total, the major item being 42 per cent from heart disease. In contrast, in 1927 cardiovascular-renal diseases

From the Metropolitan Life Insurance Company, New York, N. Y.

Presented by Dr. Shepard in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

accounted for only 34 per cent of the total, and heart disease for only 17 per cent.[4]

In the Metropolitan's own experience in 1954,[5] based upon 1948 data,[6] showed that for cardiovascular diseases this probability at age twenty for white men was 59 in 100.[6]

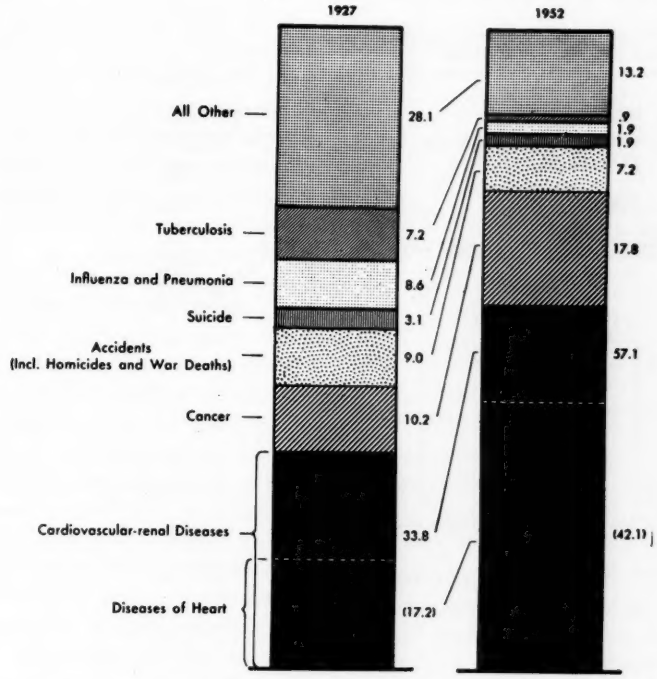


Fig. 1. Per cent distribution of death claim payments by cause of death. Ordinary insurance. (All companies reporting to Life Insurance Association of America).

of the total of $367,000,000 disbursed on account of deaths, 207 millions were accounted for by diseases of the cardiovascular-renal system. Of the total, more than 140 millions were paid specifically for deaths due to arteriosclerotic and degenerative heart disease and arteriosclerosis.

These figures present the current picture. It is important also to look at the over-all picture as measured by the chances of eventually dying from diseases of this nature. Under conditions prevailing in the general population in recent years, the chances of a white man aged twenty dying eventually from chronic or degenerative diseases are 87 in 100.[4] Twenty-five years earlier, this proportion was 75 per cent. The major items contributing to these high figures are diseases of arteriosclerotic origin. The latest analysis of this type by specific causes of death,

Morbidity from Heart Disease (Non-rheumatic)

Detailed statistics on morbidity from life insurance company records are only now beginning to be developed. Consequently, available figures are rather fragmentary. Among our own employees, disability due to heart disease, excluding rheumatic heart disease, accounted for 8 per cent of the disabilities lasting eight days or longer among men during 1954, but for 20 per cent of the time lost. At ages over fifty-five the number of cases of disability from heart disease was about one-eighth of the total, but the time lost was more than one-fourth of the total. A recent study of causes of hospitalization among the male personnel at ages sixty and over showed that diseases of the cardiovascular system accounted for more than 40 per cent of the non-surgical cases.[7]

Trend of Mortality—Cardiovascular-renal Disorders

Let us look next at the available information on the trend of deaths from cardiovascular-

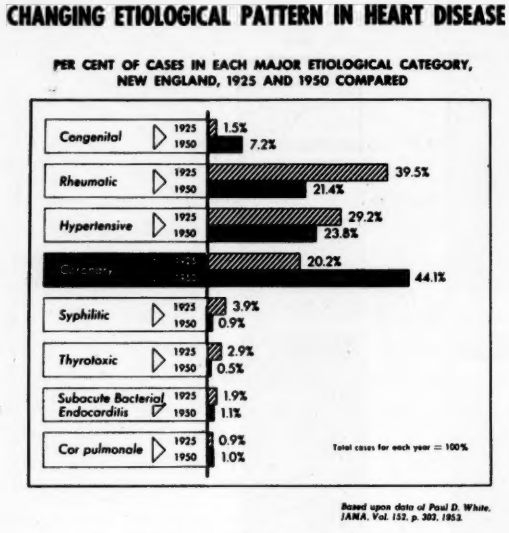


Fig. 2. Changing etiological pattern in heart disease.

renal disease in life insurance experience. For this purpose I cite the long-term series of death rates among *industrial* policyholders of the Metropolitan Life Insurance Company. The facts given here will be based upon death rates adjusted to allow for changes in the age distribution and upon rates specific for age, in order to eliminate the effect of the increasing population of older persons on the situation. Among white males at all ages combined the death rates have shown a generally downward trend, although the rate of decline has been rather small in recent years. At ages 45 to 54, however, there has been scarcely any improvement among males during the past two decades. In contrast, the trend for females, regardless of age, shows distinct improvement over this period.

Arteriosclerotic Heart Disease

It is of interest next to look at the available facts on heart disease specifically in terms of etiology as revealed in our claim records. This is brought out in an analysis of claims among *industrial* policyholders of the company in 1950-1952.[8] Among males at as early an age as thirty-five, arteriosclerosis is the predominant type in these fatal cases and accounts for more than 60 per cent of the cardiac deaths at ages beyond thirty-five. In addition, many of the cases classified as hypertensive are associated with arteriosclerosis, and many of those lacking information on etiology are probably of arteriosclerotic origin.

One of the gravest aspects of this whole problem is the excessive mortality among males. This shows up in fairly early adult life. Whereas in the experience among our *industrial* policyholders, the age adjusted mortality rate at all ages combined from arteriosclerotic heart disease among males is about two and a half times that among females, the ratio at ages 35 to 44 rises to 6 to 1.[8]

Unfortunately, the classification of deaths by cause in the past was rather inadequate as regards etiological factors. Accordingly, for earlier periods there are no data comparable to those just given. Perhaps the best and most succinct presentation of the changing etiological pattern in heart disease over the last quarter of a century is that portrayed in the figures published by Dr. Paul D. White a couple of years ago.[9] This is shown in Figure 2, which is based upon data obtained from cooperating physicians in New England on cardiac patients seen in clinic and private practice. The major change is a doubling of the proportion of cases due to arteriosclerosis to a point where it comprises nearly half the total cases seen.

While much thought has been given to the factors underlying the relatively unsatisfactory state of affairs as regards arteriosclerotic diseases, we have very little objective proof as to what has brought it about. Several hypotheses have been formulated, but these still require careful and prolonged testing.

Relation of Body Build to Mortality

In the circumstances, it might be thought that means of prevention and control of arteriosclerotic disorders would be out of the question. This is not altogether true. At least one important resource is available to us, as revealed by the experience of life insurance companies. This experience is embodied in a series of studies made at irregular intervals going back to the beginning of the century, the first of which included cases insured as early as the years immediately after the Civil War. These studies, it should be emphasized, are essentially long

term follow-up studies involving observations on large numbers of persons. All of them have shown consistently that overweights have a mortality significantly higher than persons of lesser

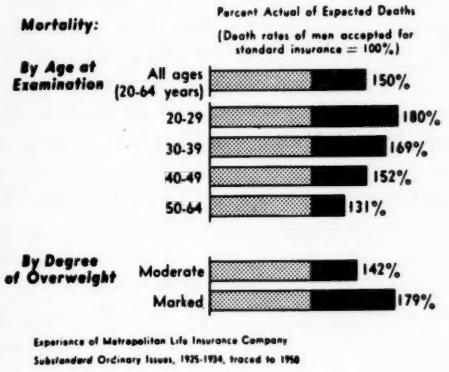


Fig. 3. Mortality of men rated for overweight.

weight, and that this excess mortality is primarily due to cardiovascular diseases. The labels used in describing these cardiovascular conditions have changed over the years, but the pattern of mortality from them is most consistent.[10]

It will suffice to illustrate the point from the recent experience of the Metropolitan Life Insurance Company based upon approximately 50,000 men and women who were charged an extra premium for their life insurance simply because they weighed too much.[11] These persons were first class risks in all other respects and were in safe occupations. The experience covers the period 1925 to 1950. As Figure 3 shows, the mortality among the men in this experience was 50 per cent higher than that among men accepted for standard insurance, that is, insured at the usual premium rates. The mortality was significantly above normal in every age group at issue of the insurance. Furthermore, mortality increased with the degree of overweight. The overweight women in the study showed about the same degree of excess mortality as compared with female standard risks.

In both sexes the bulk of the excess mortality was due to cardiovascular-renal diseases, primarily of arteriosclerotic origin. As in earlier studies, the greatest relative excess was in the mortality from diabetes, and today this primarily reflects the premature development of arteriosclerotic complications among diabetics.

Effect of Weight Reduction

Even more significant are the findings in a supplementary study of this experience.[11] We were able to identify those persons who because of reduction in weight were subsequently granted insurance at standard rates. As Figure 4 shows, the mortality among such persons was appreciably lowered—about one-fifth among the males and one-third among the females. A prime contributing factor was the reduction in the relative mortality from heart disease.

Experience on Persons Rated for Moderate Obesity Who Received Lower Ratings After Weight Reduction Compared with General Experience on Cases Rated for Moderate Obesity.

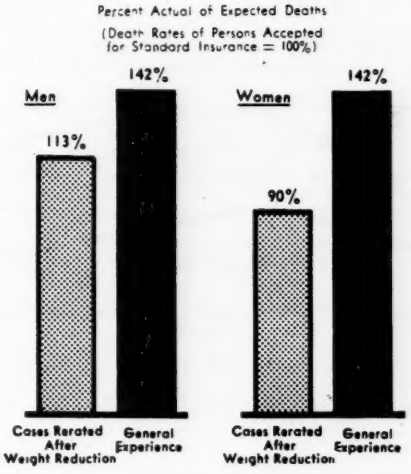


Fig. 4. Effect of weight reduction on mortality.

So far as we have been able to ascertain, this is the first objective and measurable evidence of the benefits of weight reduction among presumably healthy overweights, although the medical literature contains many statements, based upon clinical impressions, on the improvement in the physical condition of overweight patients who have reduced. There are some more specific clinical studies of such effects on persons with various types of impairments which have a bearing on arteriosclerosis. Thus, the studies of Newburgh at the University of Michigan Hospital, which are summarized in Figure 5, have shown that reduction in weight of obese diabetics greatly improves glucose tolerance to the extent that even those on insulin may get along with a lower dosage or even get along

without insulin altogether if the weight is kept down.[12] Parallel results have been reported by others. Such diabetics who regain weight show a loss of tolerance and frequently an increase

Change in Tolerance	Number of Patients
Total	47
Became normal	36
Improved	5
Unimproved	6

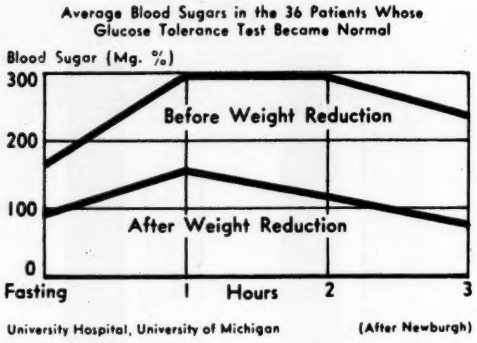


Fig. 5. Glucose tolerance test results among obese diabetics after reduction to normal weight.

in insulin dosage.[13] Studies have likewise been made of the effect of the reduction of weight in hypertensives.[14,15] These have shown a lowering of the blood pressure level in many cases.

Prognosis in Heart Disease

Life insurance records of an entirely different character provide some information on the long-range outlook for men with arteriosclerotic heart disease. For example, Robb and Marks[16] studied the after-history of two groups of male policyholders of the Metropolitan Life Insurance Company who had total and permanent disability from heart disease and were eligible for certain insurance disability benefits on that account. The first group consisted of 540 men admitted to disability between 1934 and 1936 who were traced to the anniversary of admission in 1952. Thus, for them there is a minimum follow-up period of more than fifteen years. The second group consisted of 649 who had recovered from such disability between 1925 and 1949 and traced to the 1952 anniversary; for them the period of follow-up ranges from a minimum of three years to more than twenty years.

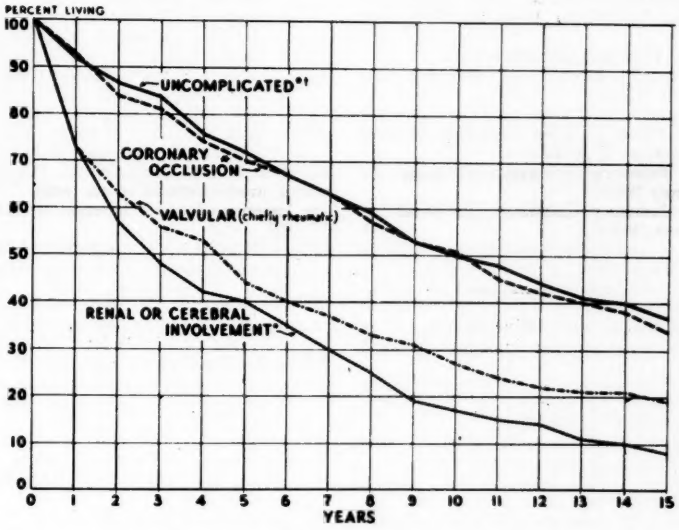
Figure 6 shows the survivorship record of the cases admitted to disability in 1934-1936. Of those with arteriosclerotic or hypertensive heart disease who had no other vascular or no renal complications and who at the time of admission to disability had not experienced an acute coronary episode, about half survived ten years or longer after becoming disabled, and more than a third were living at the end of fifteen years. The presence of cerebral or renal complications adversely affected the results, but even in this group 40 per cent survived five years, and 17 per cent, ten years or longer. The proportion of survivors was generally greater for men who were between 40 and 49 when disabled than for those who were 50 to 64. The difference, however, was less than expected when account is taken of the normal difference in mortality by age.

The recovered cases were classified somewhat differently in that attempt was made to segregate those disabled specifically as a result of arteriosclerotic heart disease. These cases were further subdivided according to the presence or absence of occlusion and also according to the reported presence of hypertension. It was found that among cases with occlusion, where there was no record of hypertension, the proportion surviving at the end of five years was 80 per cent, and at the end of ten years nearly 60 per cent. The record was somewhat poorer among cases with known hypertension. The smaller experience on cases without a history of occlusion was on the whole somewhat better.

Among the recovered cases with a history of occlusion, the survivorship record was slightly better for those fifty and over at recovery than for those between ages 40 and 49. The reverse was true in cases without a history of occlusion but this experience was smaller in volume. When comparison is made of the two age groups according to the presence or absence of a history of occlusion, it is found that on cases with occlusion the survivorship record was as good as that in cases without occlusion up until the fourth year. Subsequently the latter showed the higher survivorship rate. At ages fifty and over the results in the two groups were generally similar.

While the mortality in all of these groups, as compared with that of standard risks generally, is very considerably elevated, neverthe-

less, it is clear that a significant proportion of these men do live many years after the attack and often are able to resume a reasonably good level of activity, even to the extent of going back to work and continuing at it.



*Arteriosclerotic and hypertensive.
†Excluding those with coronary occlusion and with renal or cerebral involvement.

Fig. 6. Survivorship of white men disabled by heart disease. Metropolitan Life Insurance Company, Ordinary Department, disability cases reported and/or admitted in 1934-1936 and traced to anniversary in 1952.

These results are in substantial conformity with those based upon the experience of the Mutual Life Insurance Company, as reported by Waldron and Constable.[17] They confined their study to cases of proved myocardial infarction causing disability. The diagnosis was based for the most part on electrocardiographic findings. Their study, which covered the period 1934-1949, included 1,551 cases. The subsequent mortality was unquestionably high. The average expectation of life for those 30 to 39 at onset was estimated at 11.5 years; for those 40 to 49 at onset, it was 10.5 years; and for those 50 to 60 at onset, 8½ years. All these figures are much below the average for the age but are distinctly counter to the widely-held concept that the remaining lifetime of persons following myocardial infarction is very brief.

Summary

To sum up, the insurance industry has a real stake and real concern in the problem of arteriosclerosis, because arteriosclerosis is responsible for more deaths than any other form of cardiovascular disease, and is frequently a deleterious factor in other disorders characteristic of middle and later life. An earnest of the deep and continued concern of the industry in this problem is the establishment of the Life Insurance Medical Research Fund, the resources of which during the ten years since its founding have been devoted entirely to problems in the field of cardiovascular disorders. Insurance records are a usable and accessible source of information on many aspects of the problem, especially from the long range point of view, and have been the basis of many important scientific studies. I have reported here what our mortality and morbidity records reveal with respect to the dimensions of the problem, its characteristics and its trends. I have cited life insurance studies which have shown that, as a practical measure, control of body weight is probably the most significant and readily available approach in attacking the premature development of arteriosclerotic disease. These records have provided the best available and most concrete evidence that weight reduction pays. I have been able to give you also from our studies of life insurance records, facts on

the longevity of persons with arteriosclerotic heart disease that have been useful both to physicians and public health workers.

References

1. Life Insurance Medical Research Fund: Ninth Annual Report, July 1, 1953 to June 30, 1954, New York.
2. Dieuaide, F. R.: Personal communication.
3. Institute of Life Insurance: Life Insurance Fact Book, 1955. New York.
4. Lew, E. A.: Some implications of recent changes in mortality. Tr. Assn. of Life Insurance Medical Directors of America, 37:4, 1954.
5. Metropolitan Life Insurance Company: Statistical Bulletin, 36:6 (April) 1955.
6. Metropolitan Life Insurance Company: Statistical Bulletin, 32:4 (June) 1951.
7. Metropolitan Life Insurance Company: Statistical Bulletin, 36:3 (May) 1955.
8. Metropolitan Life Insurance Company: Statistical Bulletin, 35:2 (May) 1954.
9. White, P. D.: Changes in relative prevalence of various types of heart disease in New England. J.A.M.A., 152:303, 1953.
10. a. Rogers, O. H.: Build as a factor influencing longevity. Proc. Assn. Life Insurance Medical Directors of America, 1:280, 1906.
    b. Actuarial Society of America: Specialized Mortality Investigation. Experience of Thirty-Four Life Companies upon Ninety-Eight Special Classes of Risks. New York: 1903.
    c. Association of Life Insurance Medical Directors and Actuarial Society of America: Medico-Actuarial Mortality Investigation. Vol. II. Influence of Build on Mortality Among Men. New York: 1913.
    d. Association of Life Insurance Medical Directors and Actuarial Society of America: Medical Impairment Study, 1929. New York: 1931.
    e. Dublin, L. I., and Marks, H. H.: The build of women and its relation to their mortality. Proc. Assn. of Life Insurance Medical Directors of America, 24:47, 1937.
    f. Dublin, L. I., and Marks, H. H.: Mortality of women according to build—experience on substandard issues. Proc. Assn. of Life Insurance Medical Directors of America, 25:203, 1938.
    g. Blair, B. F., and Haines, L. W.: Mortality experience according to build on standard insurance in the Provident Mutual. Tr. Actuarial Society of America, 50:48 (May) 1949.
    h. McCormick, D. N.: Discussion of mortality experience according to build on standard insurance in the Provident Mutual. Tr. Actuarial Society of America, 50:200 (Nov.) 1949.
11. Dublin, L. I., and Marks, H. H.: Mortality among insured overweights in recent years. Tr. Assn. of Life Insurance Medical Directors of America, 35: 235, 1952.
12. Newburgh, L. H.: Control of the hyperglycemia of obese "diabetics" by weight reduction. Ann. Int. Med., 17: 935 (Dec.) 1942.
13. Osserman, K. E., and Dolger, H.: Obesity in diabetes: a study of therapy with anorexigenic drugs. Ann. Int. Med., 34:72 (Jan.) 1951.
14. Adlersberg, D.; Coler, H. R., and Laval, J.: The effect of weight reduction on a course of arterial hypertension J. Mt. Sinai Hospital, 12:984 (Jan.-Feb.) 1946.
15. Ley, H. A.: The effect of change in weight on blood pressure as shown in a study of 3,516 examinees. Proc. Life Extension Examiners, 1:33 (March-April) 1939.
16. Robb, G. P., and Marks, H. H.: What happens to men disabled by heart disease. Tr. Assn. of Life Insurance Medical Directors of America, 37:171, 1953.
17. Waldron, F. A., and Constable, W. P.: Myocardial infarction—a mortality study. Tr. Assn. of Life Insurance Medical Directors of America, 34: 69, 1951.

NATIONAL HEART INSTITUTE

(Continued from Page 735)

patient will depend upon a continuing supply of trained young men and women.

Another important approach to problems of arteriosclerosis has been through the heart disease control program. Funds are here made available through awards to state and territorial departments of health for the prevention, diagnosis, and treatment of diseases of the heart and circulation. Through this program, the health officer of the community is assisted in the development of needed health facilities. Working with local medical, scientific, and community organizations, the health officer can tailor a program to the specific needs or potential of the local community. It is through this workshop of the city, county, and state that the health needs of the individual are expressed and the final results of scientific investigation put to the acid test. The health officer and the community health program are thus aided in working with the individual, who is after all the beginning and the end of all health programs.

Thus, by the conduct and support of research and training and public health activities, the role of the National Heart Institute in meeting the challenge of arteriosclerosis, and other cardiovascular problems, is played. In principle, in law, and as administered, this role has been conceived and carried out as one of partnership in a great nationwide endeavor against diseases of the heart and circulation. Those concerned with the National Heart Institute in 1948 when it was established were proud to see it join the federation of interests then mobilizing for a comprehensive effort against heart disease. Those concerned with it today are, I believe, just as proud of the gains the partnership has won against arteriosclerosis and of the strong promise of greater advances in the coming years.

Strategy and Tactics of Research in Arteriosclerosis

IRVINE H. PAGE
Cleveland, Ohio

IN the past decade research has become almost "big business." And during this period research in arteriosclerosis has expanded phenomenally. It is an interesting commentary on physicians and investigators that the most common fatal disease known to man, described 5,000 years ago in Mesopotamia, is only now being studied, not merely from the viewpoint of its effects, but its causes and mechanisms. Clinicians have been content too long to observe its ravages without even a nod given to attempts at understanding the why and how of the disease. It seems that a latent period of 4,990 years is a pretty fair one.

Where are we in our efforts to understand arteriosclerosis? Well, certainly not very far. Discovery in general can, I think, be divided into four stages. The first is the period of uncoordinated fact collecting — the naturalist or "butterfly net" period. This is the period of magnificent indifference; in it lie the seeds of discovery but the inner structure is barely discernible. The second is the period of controversy—the "rhubarb stage" of the ball game. This stage is often called one of "scientific controversy" to make it sound less like the rhubarb that it really is. It has the merit that there is probably something worth arguing about if this stage is reached. It is healthy so long as young investigators understand its nature and not take it, or themselves, too seriously. The third is the period of definition and clarification—the "white of an egg stage" because someone clarifies the problem by precipitating the irrelevant sediment. The fourth and last is the period of solution or fruition—the "bravo stage" in which everyone, or nearly everyone, agrees, applauds and goes home and from then on nobody does much more about it, except in some rare cases, collects royalties.

I think you will agree that research in arteriosclerosis stands about half way between the first and second stages.

There are other adjuncts of modern methods of discovery, some of them often sneered at as mere trappings by our colleagues but most of them eagerly sought after once they have come into being. I refer to societies, committees and even to money, all the paraphernalia associated with that dreadful creature, the politician, and even worse, in the malignant form of the medical politician.

Again the field is bestirring itself because it now has the American Society for the Study of Arteriosclerosis to represent it and provide the rostra necessary to the communication of one's own work. The society has been, as many of you know, extremely successful. The meetings have steadily increased in quantity, but more importantly, in quality. Like so many young fields there is the usual tendency to scientific opportunism, i.e., dropping everything you are doing to get on board every new band wagon as it comes along. There is the usual re-doing by fancier methods of some of the older chestnuts. Pedestrian research is present but not in too depressing volume. Nonetheless, on the whole, it has seemed to me that sound ideas and good workmanship have prevailed and that the crackpots, exhibitionists, and opportunists seem to have been kept reasonably under wraps. The American Heart Association provides still another rallying point for those more concerned with the clinical effects of arteriosclerosis. This interest is especially focused in its Council on High Blood Pressure Research and Section on Circulation. As the section on basic science matures, it is more likely to take an interest in the mechanisms of arteriosclerosis. A time may come when it will be desirable for the American Heart Association and the American

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

Society for the Study of Arteriosclerosis to fuse their interests. In my opinion it is not yet. But the American Heart Association does something more that is important; it collects and spends money for the support of research in arteriosclerosis. This I need not detail to you because you are all familiar with its extent and because many of you are recipients. Thus, a certain amount of power and responsibility accrue to this organization. I say this because of my "original" observation, made thirty years ago, of the positive chemotactic effect of the dollar on scientists.

Hand in hand, and I might say, hand in pocket with the American Heart Association, is the United States Public Health Service as specially represented by the National Heart Institute and the National Advisory Heart Council. Dr. James Watt, its able director, has told you of its activities. Having been intimately associated for a number of years with this organization and now having no ax to grind, I will say that no more honest, hard working and intelligent group have I seen. It is only a pity all government agents aren't like them, or are they? Perhaps more than our contacts with internal revenue would lead us to think. Oddly, the great pile of brick at Bethesda that houses their intramural program is productive due, I think, to the accumen of men like Dr. Sebrell, Dr. Van Slyke and Dr. Shannon, who chose their investigators well. I say "oddly" because most of us deplore the greater and greater size of so-called "research centers." The atmosphere of bigness itself often overwhelms and obliterates the creative one in which discovery is so apt to occur. The responsibility of these tax supported investigators is great and because they are tax supported they will have the added burden of minding their scientific manners, possibly more than most.

These institutions constitute the major agencies supporting research in arteriosclerosis. Other sources should be concerned more than I think they are. For example, the dairy industry may well find itself very much involved and perhaps like the tobacco industry, it will show signs of waking up to its responsibilities very late in the game. I would hesitate to think what this great industry would have to say about our chairman's views on the fat content of the diet. The insurance companies, involved to the extent of billions of dollars, have given only token assistance, much less than a million dollars annually for research in all cardiovascular diseases.

There are other aspects of the strategy and tactics of research in arteriosclerosis, equally, or more important than, the dollar. The chief of these is the creation of an environment which is attractive and intellectually satisfying for the basic sciences. If research in this field is forever dominated by clinicians, vigorous growth cannot be expected. It is to the chemists, biophysicists, physiologists, pharmacologists, pathologists and the like that we must look. To build the needed laboratory facilities is easy but to build the intellectual and social environment in a world dominated by physicians is far from it. And this is no reflection on physicians; it is simply that they have not yet learned how to give their support to research without keeping strings on it which allows them to control the work, if not in fact, at least by indirection. The scientist is not allowed his self-respect; he is made to feel he is permitted the privilege of work at the clinician's behest.

This may sound trivial to you but from long experience I can assure you it is not. The most virulent cases of Ph.D.itis occur in those associated with physicians. To me one of the really important aspects of the basic science section of the American Heart Association is that it was set up exclusively for the purposes of scientists. Unfortunately even it hasn't found the secret yet of luring and holding the chemist's and physicist's interest and affection. In twenty years I would hope that scientists of all variety will occupy important positions in all parts of the American Heart Association. If we are willing to spend millions of dollars on them, and this would presumably indicate our belief in them, then we should be willing to make them participants in the management and future planning of our endeavors. There are a host of problems such as long term support, overhead to institutions, fluid funds, annuities, public responsibilities, et cetera, which need their wisdom. Their participation will teach them in turn some of the realities of life, spread the burden of research management and help to create that necessary atmosphere of discovery of which I spoke.

It could be hoped that the planning of the

attack on arteriosclerosis would be aided by cooperation of investigators with industry. This is in some cases true and is almost certain to lead to valuable results. Unfortunately another large group of companies are seizing upon the vast economic importance of the problem and our gross ignorance of both diagnosis and treatment, to sell all sorts of nostrums. These mixtures are purveyed not only as preventives for the "degenerative diseases of old age" but as out and out cures for arteriosclerosis. I think you are all too familiar with the "health and vigor" in the "second forty years" types of advertising.

Mixtures of androgens, estrogens, vitamins, lecithins, minerals, adrenal hormones, thyroid, ephedrine and liptropes purport to provide all the ingredients for not getting old and if taken from thirty-five to forty years of age are almost "guaranteed" to achieve both "subjective and objective" improvement. You are also familiar with the list of somewhat dubious references to the literature, either published in not well recognized journals, presented at meetings or not really pertinent to the argument. In short, the evidence to back the claims are shabby in the extreme. I have often asked the representatives of the drug houses if they would substitute the name cancer for the vague terms degenerative or circulatory disorders, etc., and see if the claims would be equally appealing. No, this is an abuse and those reputable companies who do this sort of thing should be made to understand that the peddling of these unproven mixtures adds nothing to their luster and takes many dollars needlessly from our patients. The same dollars put into sound research would yield dividends which no company would regret.

I can't let this opportunity go without a word about a new and vital problem facing the field of arteriosclerosis. It concerns suggestions, and indeed, recommendations, emanating from investigators in the field, for this or that change in the way of life of our citizens calculated to prevent arteriosclerosis. Good and wise public relations means the most careful screening and checking of all recommendations for widespread changes in public behavior. Are we in a position to recommend dietary changes yet? Are there laboratory tests yet available for the measurement of atherogenesis? Are any of the agents on the market purporting to be prophylactic or therapeutic of proved value?

And now the strategy and tactics of research in the problems of arteriosclerosis. I would be brash indeed, if I assayed to give you such. I can only give you a few of my opinions as an individual investigator. No one dares, I hope, hand down from the heights, even if he can get there, plans for the future of research.

As many of you know, I personally like to think of the problem as multifaceted. It is not alone one of lipids but of proteins and carbohydrates as well. It is not a question alone of lipoproteins in the blood but one of the reaction of the blood vessels to these lipoproteins as well. To me the problem is much like that of a public water works. Plasma with a wide variety of physicochemical properties is being pumped around in conduits which act as filter beds. The conduits are of widely varying properties so we have at least two large groups of variables. And then there are the pressure and flow relationships which seem important and highly variable. And finally there are a host of secondary factors such, for example, as peculiarities of anatomy which may at times become decisive in the effects of arteriosclerosis. The type of epidemiological approaches prosecuted by Keys and by Morris seem to me of great value for we must know of those environmental factors which aggravate the trouble. As many of you know, Paul White and I have seen eye to eye for many years in our desire to keep your arteries flexible by using the God-given form of locomotion. With all this in mind it is hard for me to accept the primacy of any especial approach. The only danger is that a single approach may exclude others with attendant failure to think creatively from a broader perspective. Too hasty codification of ideas ultimately leads to solidification. Ideas have a way of becoming "concrete" all too soon.

I think we must neither be surprised, nor too disturbed, when discoveries of the cause and cure of arteriosclerosis are announced reasonably regularly. But we must be eternally vigilant that privilege be preserved of freedom to speak out. With this privilege goes the responsibility of keeping emotional responses within reasonable bounds. In this we have been lax and as proof of it read your daily mail for the

(Continued on Page 808)

Pleomorphism of the Lesions of Arteriosclerosis

G. C. McMILLAN
Montreal, Quebec

HARDENING of the arteries, or rather arteriosclerosis, is a broad concept that in man encompasses pathological processes of the most varied sorts. Among the arteriosclerotic changes that may be observed, those lesions that contain an appreciable amount of lipid material in the arterial intima have been segregated from the remainder and called atherosclerotic. However, atherosclerosis itself is a very complex change that cannot be regarded as a simple pathological or disease entity. Even in the same individual the natural history of atherosclerosis from its commencement to its various complicated end states may involve many variable causal factors and developmental patterns.

Atherosclerosis is usually defined or assessed by the pathologist as a lesion. It is usually considered by the clinician to be a disease state that can be defined or assessed in the functional terms of its own complications or sequelae. It is, of course, appreciated that the sequelae may partially depend upon circumstances that are more or less independent of atherosclerosis *per se*. For example, the sequelae or complications of hemorrhage into atherosclerotic plaques, of thrombosis, of organization of thrombi and of infarction are only partially dependent upon the atherosclerotic lesion itself. Except in general terms, it is not possible to equate the lesions of atherosclerosis with their possible sequelae because the association between them is neither qualitatively nor quantitatively constant.

Ludwig Aschoff[1] has spoken of arteriosclerosis as an arterial dystrophy "which manifests itself by deposits of the most varied kinds in the vascular walls . . . " Some of these accumulate during the uncomplicated development of an atherosclerotic lesion while others may be super-added as a result of some local complication such as haemorrhage, necrosis or thrombosis at the site of a lesion. With the passage of time the material products of these complications may be incorporated in the lesion, become an integral part of it and contribute to the state of sclerosis.

I would like to illustrate for you something of the pleomorphism of the lesions that may be observed in arteries when a pathological or clinical diagnosis of simple or complicated atherosclerosis is made. Most of the material is from the major coronary arteries of man since these are of the greatest practical interest. The slides illustrate something of the natural history of the condition.

(*The colored slides that were shown with this paper could not be reproduced here. However, a brief description of each slide is presented to indicate the material that was covered.*)

1. *Coronary Artery.* Fat stain. To illustrate two large lipid-rich atheromatous lesions and marked stenosis of the lumen. In spite of the large content of lipid there is also a large amount of fibrous tissue present constituting at least one half of the bulk of the lesions.

2. *Coronary Artery.* Fat stain. A large crescentic atherosclerotic plaque narrows the lumen to about one half its normal size. The plaque contains a small amount of lipid at its junction with the media, but the majority of the lesion is fibrous and does not contain visible fat.

3. *Coronary Artery.* Fat stain. To illustrate a common association of a moderate amount of lipid, some macrophages and round cells and a moderate amount of fibrosis. Small vascular channels can be seen within the atherosclerotic intimal thickening. An uncommon feature of this slide is the presence of lipid-rich atheromatous material in the media of the artery beneath the center of the plaque.

4. *Coronary Artery.* Fat stain. To illustrate at larger magnification the lipid infiltration of the media referred to in the previous slide.

5. *Cerebral Artery.* Fat and elastic tissue stain. To illustrate lipid infiltration of the media of the cerebral arteries occurring through a gap in the internal elastic membrane. The fatty material has escaped from the

From the Department of Pathology, Pathological Institute, McGill University, Montreal, Quebec, Canada.
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

intima through the elastic tissue defect into the media and to the adventitia. This type of lesion is common in cerebral arteries.

6. *Cerebral Artery.* Elastic tissue stain, paraffin section. To illustrate a lesion similar to that observed in the previous slide. The lesion has an hour-glass or button-hole shape. Lipid-filled macrophages or foam cells extend to the junction of media and adventitia.

7. *Coronary Artery.* Fat stain. Polarized light. To illustrate an accumulation of crystalline cholesterol material in an atherosclerotic plaque. This accumulation unlike most, contains only a very small amount of sudanophilic fatty material. It is surrounded by fibrous tissue.

8. *Crystals.* Polorized light. Crystals of cholesterol obtained by extraction with solvents from an atherosclerotic aorta. The crude material was purified slightly and recrystallized slowly. The notched square platelike shape is characteristic. The unusual color effects are due to retardation of light.

9. *Surface Preparation of Aortic Endothelium.* Silver, sudan and hematoxylin stain. To illustrate an approximately normal endothelial pattern (female, aged seventeen years; congenital aneurysm of cerebral artery with rupture).

10. *Surface Preparation of Aortic Endothelium.* Silver, sudan and hematoxylin stain. To illustrate a bizarre endothelial pattern with the formation of multinucleated and giant endothelial cells. Such changes, like those of atherosclerosis, are associated with increasing age, but it is not established that the endothelial change and an atherosclerotic change are intimately related (male, aged forty-three).

11. *Surface Preparation of Aortic Intima.* Chlorazol black E stain. To illustrate some aspects of the proliferating reactive tissue in the atherosclerotic intima. The large bizarre stellate cells are probably smooth muscle cells. They lie among fibroblasts and numerous large and small round mononuclear cells.

12. *Surface Preparation of Aortic Intima.* Chlorazol black E stain. Polarized light. Another area of atherosclerotic intima composed largely of fibroblastic and collagenous elements with no muscle cells and few round cells. Lipid material is seen as bright, glistening droplets in large stellate cells. None of the more common globular lipid-filled macrophages or foam cells are present.

13. *Surface Preparation of Aortic Intima.* Silver, sudan and hematoxylin stain. Another area of aortic intima illustrates a focus where numerous large and small mononuclear round cells have collected under the endothelium in the intima. Only minute amounts of fat are present.

14. *Coronary Artery.* Hematoxylin eosin stain. This profoundly stenosed artery is from a 14-year-old female who suffered from nephrosis and chronic nephritis with hypercholesterolemia. The lesion shows a profound atrophy of the arterial media which is attenuated almost to complete disappearance. Fibrous tissue has proliferated to almost occlude the vessel. It contains moderate amounts of lipid but is not excessively fatty. Some lipid has penetrated to the adventitia.

15. *Coronary Artery.* Hematin-phloxin-saffron stain. The arterial intima contains two superimposed atherosclerotic lesions. The outer one is somewhat calcified. Both are heavily embedded in fibrous tissue. The lumen is stenotic. Adjacent lies a small extramyocardial branch of the coronary tree. It is almost obliterated by connective tissue proliferation.

16. *Coronary Artery.* Hematin-phloxin-saffron stain. To illustrate the complication of haemorrhage into a relatively non-fatty atherosclerotic lesion. Thrombosis has not occurred at this particular site. The products of the haemorrhage will contribute to the sclerosis at the site.

17. *Coronary Artery.* Hematin-phloxin-saffron stain. To illustrate the complication of intramural haemorrhage with disruption of the atherosclerotic plaque and thrombus formation.

18. *Coronary Artery.* Larger magnification of vessel shown in Slide 17. Haemorrhage has disrupted a pultaceous fatty plaque. Cholesterol crystal clefts are numerous. Thrombus material is seen where the plaque has broken into the lumen. There is some clotted blood attached to the thrombus.

19. *Coronary Artery.* Hematoxylin-eosin stain. To illustrate atherosclerosis complicated by thrombosis and organization of the thrombus. There is a small lumen surrounded by dense collagenous tissue. The majority of the occlusive lesion is composed of loose myxomatous connective tissue.

20. *Coronary Artery.* Hematin-phyloxin-saffron stain. Illustrating arteriosclerosis complicated by thrombosis. The arteriosclerotic intima shows extensive fibrotic, hyalin and calcific changes. Thombosis has occurred and a rather acellular "jelly" or hyalin material has replaced it. Large thin-walled revascularization channels have been formed.

21. *Coronary Artery.* Larger magnification of Slide 20. To illustrate the relatively acellular jelly-like material that has replaced the thrombus.

22. *Coronary Artery.* Hematin-phloxin-saffron stain. To illustrate atherosclerosis complicated by thrombosis. There is fibrosis, hyalinization and calcification in the intima. Thrombosis has occurred and extensive organization and recanalization has replaced the thrombus material.

23. *Coronary Artery.* Larger magnification of Slide 22. To illustrate the fibroblastic and collagenous nature

of the reorganized mass. There is extensive development of smooth muscle about many of the channels of revascularization.

24. *Coronary Artery.* Hematin-phloxin-saffron stain. To illustrate complete occlusion of an artery by a large amount of hyalin fibrous tissue and equally extensive deposits of calcium salts. Very little lipid is present. The vessel has been rendered extremely sclerotic.

The lesions you have seen are more or less common in the experience of the pathologist. They are very different one from another and manifest many vagaries of composition and content. They represent the lesions that one seeks to prevent or to cure. The features common to almost all of the lesions are the presence of mixed lipid material in the arterial intima, a cellular reaction manifest by the presence of large and small round cells—that is, macrophages, lymphocytes and indifferent mononuclear cells, and a proliferation of fibroblastic tissue. The proportions of these various elements to each other is rather unpredictable. Upon these common features may be superimposed a variety of degenerative changes such as necrosis; hyaline, fibrinoid or mucoid degeneration; and pathological calcification. Further changes may incorporate products of blood or thrombus material in the lesions. Cellular reactions may attempt to form new vascular channels that may develop abundant smooth muscle, connective tissue and endothelium within the original lumen of the artery. Varying forms and degrees of sclerosis of the vessel result.

The conclusions to be drawn from the lesions that you have seen are, in one sense, very simple. It is obvious that no simple etiological or pathogenetic concept will explain fully the pleomorphism of the lesions. According to our current understanding of the development of atherosclerosis, the most important single etiological factor is the abnormal focal accumulation of lipid material in the arterial intima. The lipid accumulation is followed by an irritative and proliferative cellular reaction in the intima and this in turn may be succeeded by the most varied degenerative changes in the lesions, by haemorrhage and by thrombosis.

From the prophylactic point of view one may seek to prevent or at least lessen not only the lipid deposition but also the subsequent proliferative and degenerative stages of the development of atherosclerotic lesions as well as the possible occurrence of intramural haemorrhage or thrombosis. Theoretically there is no compelling reason to maintain that an approach to the prevention of atherosclerotic disease must be limited solely to those aspects concerned with lipid accumulation, although this is obviously a valuable approach that lies close to the root of the matter.

From the point of view of the cure or removal of advanced or clinically important lesions the pleomorphism that you have seen precludes any simple metabolic approach. The composition of such lesions is so variable from person to person and from lesion to lesion that any metabolic procedure directed towards removal or reduction of one constituent, while possibly beneficial, cannot be expected to remove all of the other components; in any case, the nature of the major components of the lesions may not be known.

It is apparent from a pathological examination of a variety of simple and complicated atherosclerotic lesions that the prevention of the lesions is, in theory, a very different matter than their removal. Consideration of the prevention of a sequel such as thrombosis has still different theoretical bases.

Reference

1. Aschoff, Ludwig: Introduction in: Arteriosclorsis, a Survey of the Problem. Ed., E. V. Cowdry. New York: The Macmillan Co., 1933.

HEART-TY APPETITE

It has long been recognized that obesity produces detrimental effects on cardiac patients. Overweight heart patients have a much higher mortality rate. Additionally, "Obese people often have symptoms suggestive of heart disease, but without any demonstrable cardiac abnormality. . . . Obesity reduces work tolerance and cardiac reserve; it increases oxygen consumption, cardiac work, blood pressure and cardiac rate." Conversely, "Undernutrition lightens the work of the heart and has been of benefit to those with heart disease, . . ."—MASTER, A. M., and JAFFE, H. L.: Physiological Effects of Obesity Upon the Heart, *Journal of the American Geriatrics Society*, 3:299 (May) 1955.

Factors Other than Cholesterol in Arteriosclerosis

WILLIAM B. WARTMAN
Chicago, Illinois

WHEN one first begins to study arteriosclerosis experimentally, enthusiasm for one's own particular method of attacking the problem runs high. The horizon looks bright and the prospect of early success is encouraging, but before long even the most optimistic investigator becomes aware that the problem has many aspects he had not anticipated and he gradually realizes that perhaps "many roads lead to Rome." The program of this symposium, with papers on such diverse topics as metabolic disturbances, genetical effects, environmental factors and the baneful effects of our mundane way of life, clearly reflects this varigated aspect of the problem of arteriosclerosis. This catholicism of outlook and diversity of investigative approach to the problem seems to me most desirable for certainly we have not yet discovered many of the facts we must have in order to plan properly for the treatment and control of arteriosclerosis.

With these thoughts in mind I have chosen to tell you not about the discoveries made by traveling the main highway of the investigation of lipid metabolism, but rather to describe some of the discoveries made by exploring the byways of experimental arteriosclerosis. However, because of time limitations it will not be possible to consider all of these discoveries and so I shall limit myself to the following because it seems likely that they may play an important part in the pathogenesis of arteriosclerosis.

1. Ischemic Injury of the Arterial Wall
2. Metabolic Changes in the Arterial Wall
3. Thrombosis as a Cause of Arteriosclerosis
4. Vascularization and Hemorrhage of the Intima

From the Department of Pathology, Northwestern University Medical School.

Financial aid for this study from the Chicago Heart Association and from private sources is acknowledged.

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

Ischemic Injury of the Arterial Wall

For many years we have known that severe arteriosclerosis may follow injury of an artery and that often the sclerosis is sharply confined to the site of injury. Syphilitic aortitis provides a familiar example of this. Syphilis attacks chiefly the ascending part of the thoracic aorta and the arteriosclerosis which develops later also occurs in the same place—a location that is quite different from the usual site of aortic arteriosclerosis which is in the abdominal portion. Arteriosclerosis also occurs after other forms of primary arteritis such as rheumatic fever (Karsner and Bayless, 1934) and acute and chronic inflammations (Saphir and Gore, 1950). Experiments have also given confirmation of this view, showing that arterial cauterization (Ssolowjew, 1930, and Schlichter, 1946) and freezing (Kelley, Taylor and Hass, 1952) will cause localized arteriosclerosis and that rabbits fed cholesterol after arterial cauterization develop atheromas confined to the site of injury (Schlichter, Katz and Meyer, 1949; Kelley, Taylor and Hass, 1952; Ssolowjew, 1930). All these workers have independently suggested that the pathogenesis of this type of arteriosclerosis is ischemia of the arterial wall produced by injury of the vasa vasorum. Other evidence also supports the idea that local or diffuse ischemia of the arterial wall may cause arteriosclerosis. For example, in the neighborhood of infarcts of the kidney and myocardium, where the tissues are presumably poorly oxygenated, the intima of the arteries becomes greatly thickened (Rotter, 1949). Likewise, the extensive experiments of Hueper, in which he produced generalized arteriosclerosis in dogs by the administration of polyvinyl alcohol and other macromolecular substances, seem best explained on the basis of anoxia (Hueper, 1941a, 1941b).

Another mechanical factor which also ap-

pears to have an important effect on the development of arteriosclerosis is high blood pressure. This concept is well supported by clinical (Dock, 1946), pathological (Baurle, 1951; Blumenthal, Handler and Blache, 1954, and Dock, 1946) and experimental evidence (Bronte-Stewart and Heptinstall, 1955; Ferguson and Varco, 1955).

Metabolic Changes in the Arterial Intima and Media

Until quite recently many students of arteriosclerosis have regarded the arterial wall as a passive participant in the development of the lesions and have placed emphasis on primary injury of the vessel by toxic substances in the blood stream. Now, however, evidence has accumulated which suggests that abnormal metabolic processes within the arterial wall itself may be of primary importance. For example, the results of experiments in which P^{32} was injected into cholesterol fed rabbits indicate a marked derangement of phospholipid metabolism in the aorta. Phospholipid was formed five times faster in the atheromatous than in the normal aorta and seemed to be synthesized in the wall of the vessel itself (Shore, Zilversmit and Ackerman, 1954). Other experiments, using P^{32} and acetic acid in which both carbons were labeled with C^{14}, indicate that the surviving aorta of rats can convert acetate to fatty acids and also readily incorporate P^{32} into the phospholipid molecule (Chernick, Srere and Chaikoff, 1949). Such experiments suggest that arterial tissue may actively metabolize lipids. However, we can not yet consider this suggestion as proved, for other experiments with Tritium labeled cholesterol indicate that exogenous cholesterol forms the bulk of the atheromatous deposits in cholesterol fed rabbits (Biggs and Kritchevsky, 1951).

Another interesting metabolic change occurring in the aorta concerns the metachromatic ground substance. This is a mucoid material which is thought to be an acid mucopolysaccharide and most likely chondroitin sulfate. It is probably a normal constituent of the aorta for it is present during the fetal period and at all ages thereafter in both humans and animals. Under abnormal conditions it may increase abundantly and form conspicuous deposits both in the media, where it lies closely applied to the elastic fibers and the elastic lamina, and in the intima, where it accumulates particularly in fibrous and hyalinized areas (Bunting and Bunting, 1953; Taylor, 1953).

Interest has centered around the arterial mucopolysaccharides for several reasons. In the first place, studies of early human coronary and aortic arteriosclerosis show that several pathological processes participate in its development and that they occur in an orderly sequence (Moon and Rinehart, 1952; Taylor, 1953). The first observable change consists of simultaneous proliferation of subendothelial fibroblasts, fragmentation of the internal elastic membrane and increase in mucoid ground substance. Lipid deposits form only after these changes have occurred and hyalinization and calcification appear only in the late stages. Indeed there is evidence to suggest that hyalinization of the tissues results from abnormal polymerization of the mucoid ground substance (Moon and Rinehart, 1952).

There is another aspect of the acid mucopolysaccharides that may have importance for the problem of arteriosclerosis. Accumulating evidence shows that they may be one of the tissue factors which determine the localization of cholesterol or other lipid deposits. For example, morphological observations and chemical determinations of the sulfate content of human aortas, which are a measure of the acid mucopolysaccharides, indicate that such a tissue factor probably determines the localization of the lipid deposits in hereditary xanthomatosis, syphilitic aortitis and the atherosclerosis of hypertension (Faber, 1949). In addition experiments have demonstrated that rabbits, which have been fed amounts of cholesterol insufficient to produce atheromatosis, will nevertheless accumulate cholesterol in the aorta following experimental procedures that produce reparative processes in which the acid mucopolysaccharides are increased. This has been shown in epinephrine sclerosis (Erb, 1905) and during repair of cauterized wounds of the aorta of rabbits (Ssolowjew, 1926, 1930).

Two important tools for the experimental study of the part played by the mucopolysaccharides in the pathogenesis of arteriosclerosis have recently been provided. Thus, it has been discovered that rats fed Lathyrus odoratus meal develop aortic aneurysms, and edema and hem-

orrhage of the media associated with increased chondroitin sulfate B and degeneration of the elastic fibers (Churchill, Gelfant, Lalich and Angevine, 1955). In addition, it has been found that arteriosclerosis develops in pyridoxine deficient monkeys (Rinehart and Greenberg, 1951).

Thus a considerable body of evidence indicates that an early change in human arteriosclerosis and possibly also in rabbit and fowl (Paterson, Slinger and Gartley, 1948) cholesterol atherosclerosis, has to do with an increased deposition in the media and intima of mucopolysaccharides. Other evidence also exists that the primary lesion of arteriosclerosis may occur in the media, but time does not permit my reviewing it (Gray, Handler, Blache, Zuckner and Blumenthal, 1953). In passing, I should like to comment that this aspect of arteriosclerosis has not been studied as sufficiently as the known facts indicate it should.

Thrombosis as a Cause of Arteriosclerosis

One of the most interesting new ideas about the cause of arteriosclerosis is the suggestion that thrombi, and in particular fibrin thrombi, instead of being exclusively the result of arteriosclerosis may be the cause of it. According to this concept small thrombi of fibrin or blood are deposited on the arterial intima, then organized and covered with endothelium and eventually incorporated into the arterial wall as focal, eccentric, thickened areas. Similar episodes repeated over the years eventually give rise to arteriosclerotic plaques. Rokitansky in 1852 first suggested such an explanation to account for the development of arteriosclerosis and his suggestion came to be known as the "encrustation theory." Virchow, however, repudiated this theory and as a result of his influence the encrustation theory was either forgotten or mentioned only briefly for the sake of completeness.

However, in 1946 Duguid brought forth morphological evidence which strongly suggested that under certain conditions organization of thrombi deposited on the walls of arteries did occur and that the morphological results of the organization were indistinguishable from arteriosclerosis. According to the thrombosis hypothesis when a mural or occlusive thrombus forms in an artery, it soon retracts in order to allow restoration of the circlation, and the new "channel becomes lined with endothelium and a new lumen is thus formed, with the thrombus now lying external to it and forming as it were a part of the vessel wall. Organization then follows, the subendothelial layer of fibrin on the free surface of the thrombus being transformed into fibrous tissue by what appears to be a direct metamorphosis, while around the attached surface of the thrombus a vascular zone of organization is formed which advances into the mass, converting it into fibrous tissue. Since this new tissue is similar to, and continuous with, that of the original intima, it has the appearance of an intimal overgrowth.

"In some instances a complete organization of the mass is brought about in this way; but more often, before the process has reached the center, fatty degeneration and sometimes softening take place, and thus the picture of atherosclerosis is produced. While these changes are in progress the new lumen under the influence of the blood pressure gradually widens, while the thrombus shrinks and becomes moulded to the shape of the vessel wall, so that in the end the mass which once filled the lumen is reduced to a crescentic thickening of the intima." (Duguid, 1949).

Other observers have verified Duguid's morphologic findings so that there is now little reason to doubt the accuracy of his observations or the correctness of his interpretations of their significance (Heard, 1949; Crawford and Levene, 1952; Geiringer, 1951, and Wagner, 1954). Other evidence also supports this view. For example, it has been found that in humans both large and small emboli to the lungs may undergo just such endotheliazation, organization and incorporation into the arterial wall (Krutzsch, 1920; Goedel, 1930; Ljungdahl, 1928; Belt, 1939a, b; Castleman and Bland, 1946; McKeown, 1952; Mautz and Craige, 1951; Saphir, 1932). Several authors have also described tumor emboli in the small pulmonary arteries being surrounded by hyaline thrombi that undergo organization and cause local intimal thickenings which resemble very closely pulmonary arteriosclerosis (Saphir, 1947; Krutzsch, 1920; Barnard, 1954a). In addition cases have been described in which repeated showers of fibrin emboli during pregnancy have lodged in the lungs and there undergone organization (Schneider, 1950, 1951).

This concept, that arteriosclerosis may result

from organization of thrombi, is also susceptible to experimental testing and numerous experiments have shown that under certain conditions both thrombi and emboli may, indeed, become organized and produce significant arterial disease in exactly the way Duguid described (Harrison, 1948; Wartman, Jennings and Hudson, 1951; Wartman, Hudson and Jennings, 1951; Muirhead and Montgomery, 1951; Heard, 1952; McLetchie, 1952; Barnard, 1953, 1954).

The evidence, then, clearly shows that thrombosis must be considered as a possible factor of primary importance in causing arteriosclerosis. Indeed the thrombosis hypothesis explains some of the facts that other theories do not. In the first place, the organization of thrombi of fibrin and blood can actually be observed in many cases of human arteriosclerosis. In the second place, local lesions can be easily explained although the theory does not explain why certain locations are so consistently affected. In the third place, the theory accounts adequately for the narrowing which occurs so frequently in the human form of the disease. This fact is difficult to explain on the basis of primary injury of the vessel wall since destruction of tissue and replacement fibrosis in vessels subjected to expansile movement and considerable internal pressure should lead to dilatation rather than narrowing. No other theory of the pathogenesis of arteriosclerosis accounts for this feature so well—an observation which Duguid has repeatedly made. And finally it seems likely that many and perhaps most cases of pulmonary arteriosclerosis result from organization of multiple showers of small emboli or thrombi.

At first sight the thrombosis hypothesis seems to stand apart from other concepts and even to conflict with them. But recently other lines of investigation have begun to converge with it. Especially important from this point of view is the work on fibrinolysin activity during life and on fibrinolysin and the fluidity of blood post mortem (Biggs, Macfarlane and Pilling, 1947; Mole, 1948). It is obvious that if we accept as a working hypothesis the concept of the thrombotic origin of arteriosclerosis then we must admit the importance of factors controlling the formation of fibrin in the circulating blood. Macfarlane's investigations have shown that "fibrinolysis activation in the blood during life may be the initial result of a variety of stimuli having in common the exposure of body or mind to unusual stress.

"Mole points out that during life there is a continual production of fibrinogen by the liver, that this must involve a continual removal from the blood stream, and that normally some deposition of fibrin would be expected. Having investigated the relation between fibrinolysin and the fluidity of blood at necropsies, he considers that fibroinolysin is most probably produced by the vascular endothelium and that this may be the natural physiological means of preventing undue deposition of fibrin in health. Failure of fibrinolysis will promote the deposition of mural thrombi, which may form the initial lesion in atherosclerosis. Such failure, for example, occurs often in infection and cachexia, conditions which favor thrombosis." (Brit. Med. J. 1949).

The results of the experiments of Fullerton, Davie and Anastasopoulas (1953) not only confirm this view but extend it by showing a possible relationship to the lipid-cholesterol factor. They found that lipemia is accompanied by increased coagulability of blood and suggested that cholesterol and lipemia may produce arteriosclerosis by leading to intravascular fibrin formation and the initiation of the sequence of events suggested by Duguid. All this work needs further confirmation and the many interesting possibilities suggested by these concepts need to be put to the test of controlled experimentation.

Vascularization and Hemorrhage of the Arterial Intima

Finally I wish to discuss briefly the possibility that vascularization and hemorrhage of the arterial wall may be factors in the pathogenesis of arteriosclerosis. I believe it is fair to say that most students now accept the fact that the diseased arterial wall frequently becomes excessively vascularized with thin-walled, tortuous capillaries which are prone to rupture and bleed into the intima and media. Further, much evidence indicates that an expanding hematoma within the intima causes the obstruction in a small proportion of cases of coronary occlusion while in a larger proportion of cases intimal hemorrhage precipitates massive thrombosis (Wartman, 1950, for review of older literature; King, 1952; Yater et al, 1948; Paterson, 1952; Schlichter, 1948; Geiringer, 1951; Waters, 1948;

Lindbom, 1950; Papcharalampous and Zollinger, 1953).

All of these observations have been explained on the assumption that vascularization and hemorrhage are secondary phenomena occurring rather late in the development of arteriosclerosis. However, some observers have expressed a somewhat different point of view. They have suggested that disease of the vasa vasorum with subsequent abnormal vascularization and intramural bleeding may be events of primary rather than secondary importance. Winternitz (1938) points out that arteries are normally possessed of a capillary bed and thus are able, like other tissues, to respond to injury by the two fundamental processes of exudation and proliferation. He further observes that in the case of arterial injury exudation often predominates, that the exudate is often serofibrinous or hemorrhagic and that since it cannot always be easily removed it may accumulate in the vessel wall. Later these accumulations undergo fatty degeneration, necrosis and calcification and form atheromatous plaques. Increased serum lipids might hasten or exaggerate this process, but would not be essential to it. Many different etiologic agents might start such a process—vitamin deficiencies, a hemorrhagic diathesis, or a multitude of different microorganisms. In support of this concept Winternitz also draws attention to the fact that the development of the morphologic lesions of infective endocarditis bears a striking resemblance to the development of arteriosclerosis. A similar sequence of events is also known to occur in the thyroid where degenerating and organizing hemorrhages produce lesions indistinguishable, except for location, from arterial atheromas.

I believe I have given enough evidence to indicate the attractiveness of this concept of the pathogenesis of arteriosclerosis. Certainly it seems worthy of being used as a working hypothesis for other investigations.

Summary

In this paper, I have presented evidence which indicates that causes other than disturbed lipid metabolism may also be important in the initiation and development of arteriosclerosis. These causes include ischemic injury of the arterial wall, tissue factors such as the acid mucopolysaccharides, organization and incorporation into the intima of mural thrombi, and organization and vascularization of serous and hemorrhagic exudates in the intima. Evidence obtained from observations in humans and experiments in animals indicates that each of these possibilities could be used profitably as a working hypothesis for further study of the problem of arteriosclerosis.

References

1. Barnard, P. J.: Experimental fibrin thromboembolism of the lungs. J. Path. & Bact., 65:129, 1953.
2. Barnard, P. J.: (a) Thrombo-embolis primary pulmonary arteriosclerosis. Brit. Heart J., 16:93, 1954.
3. Barnard, P. J.: (b) Pulmonary arteriosclerosis and cor pulmonale due to recurrent thromboembolism. Circulation, 10:343, 1954.
4. Bäurle, W.: Die Coronarsklerose bei Hypertonie. Beitr. z. Path. Anat. u. Allge. Path., 111:108, 1951.
5. Belt, T. H.: (a) Late sequelae of pulmonary embolism. Lancet, 2:730, 1939.
6. Belt, T. H.: (b) Autopsy incidence of pulmonary embolism. Lancet, 1:1259, 1939.
7. Biggs, M. W., and Kritchevsky, D.: Observations with radioactive hydrogen (H^3) in experimental atherosclerosis. Circulation, 4:34, 1951.
8. Biggs, Rosemary, Macfarlane, R. G., and Pilling, J.: Observations in fibrinolysis. Experimental activity produced by exercise or adrenaline. Lancet, 1:402, 1947.
9. Blumenthal, Herman T., Handler, Fred P., and Blache, J. Owen: The histogenesis of arteriosclerosis of the larger cerebral arteries, with an analysis of the importance of mechanical factors. Am. J. Med., 17:337, 1954.
10. Bronte-Stewart, B., and Heptinstall, R. H.: The relationship between experimental hypertension and cholesterol-induced atheroma in rabbits. J. Path. & Bact., 68:407, 1955
11. Bunting, C. H., and Bunting, Henry: Acid mucopolysaccharides of the aorta. Arch. Path., 55:257, 1953.
12. Castleman, B., and Bland, E. F.: Organized emboli of the tertiary pulmonary arteries. Arch. Path., 42:581, 1946.
13. Chernick, S.; Srere, R. A., and Chaikoff, I. L.: The metabolism of arterial tissue. II. Lipide syntheses: the formation *in vitro* of fatty acids and phospholipides by rat artery with C^{14} and P^{32} as indicators. J. Biol. Chem., 179:113, 1949.
14. Churchill, D. W.; Gelfant, S.; Lalich, J. J., and Angevine, D M.: Alterations in the polysaccharides and elastic fibers in the aortas of rats fed toxic lathyrus factor. Lab. Invest., 4:1, 1955.
15. Crawford, T., and Levene, C. I.: The incorporation of fibrin in the aortic intima. J. Path. & Bact., 64:523, 1952.
16. Dock, W.: The predilection of atherosclerosis for the coronary arteries. J.A.M.A., 131:875, 1946.
17. Duguid, J. B.: Thrombosis as a factor in the pathogenesis of coronary artherosclerosis. J. Path. & Bact., 58:207, 1946.
18. Duguid, J. B.: Pathogenesis of atherosclerosis. Lancet, 2:925, 1949.
19. Erb, W.: Experimentelle und histologische Studien über Arterienerkrankung nach adrenallininjektionen. Arch. f. exper. Path. u. Pharmakol., 53:173, 1905.
20. Faber, Mogens: The human aorta: Sulfate-containing polyuronides and the deposition of cholesterol. Arch. Path., 48:342, 1949.
21. Ferguson, D. J., and Varco, R. L.: The relation of blood pressure and flow to the development and regression of experimentally produced pulmonary arteriosclerosis. Circulation Res., 3:152, 1955.

22. Fullerton, H. W., Davie, W. J. A., and Anastasopoulos, G.: Relationship of alimentary lipaemia to blood coagulability. Brit. Med. J., 2:250, 1953.
23. Geiringer, E.: Intimal vascularization and atherosclerosis. J. Path. & Bact., 63:201, 1951.
24. Goedel, A.: Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie. Virchows Arch. Anat. Physiol., 277:507, 1930.
25. Gray, S. H.; Handler, F. P.; Blache, J. O.; Zuckner, J., and Blumenthal, H. T.: Aging processes of aorta and pulmonary artery in Negro and white races. Arch. Path., 56:238, 1953.
26. Harrison, C. V.: Experimental pulmonary arteriosclerosis. J. Path. & Bact., 60:289, 1948.
27. Heard, B. E.: An experimental study of thickening of the pulmonary arteries of rabbits produced by the organization of fibrin. J. Path. & Bact., 64:13, 1952.
28. Heard, B. E.: Mural thrombosis in the renal artery and its relation to arteriosclerosis. J. Path. & Bact., 61:635, 1949.
29. Huener, W. C.: (a) Experimental studies in cardiovascular pathology. III. Polyvinyl alcohol atheromatosis in the arteries of dogs. Arch. Path., 31: 11, 1941.
30. Hueper, W. C.: (b) The etiology and the causative mechanism of arteriosclerosis and atheromatosis. Medicine, 20:397, 1941.
31. Karsner, H. T., and Bayless, F.: Coronary arteries in rheumatic fever. Am. Heart J., 9:557, 1934.
32. Kelley, F. B.; Taylor, C. B., and Hass, G. M.: Experimental atheroarteriosclerosis. Arch. Path., 53:419, 1952.
33. King, Edgar S. J.: Haemodynamics of subintimal haemorrhage. Australian Ann. Med., 1:18, 1952.
34. Krutzsch, G.: Über rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien. Ztschr. Path., 23: 247, 1920.
35. Lindbom, Ake: Arteriosclerosis and arterial thrombosis in the lower limb: A roentgenological study. Acta Radiologica Supp., 80:66, 1950.
36. Ljungdahl, M.: Gibt es eine chronische Embolisierung der Lungenarterie? Deutsches Arch. f. klin. Med., 160:1, 1928.
37. Mautz, F. A., and Craige, E.: Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. Arch. Path., 52:91, 1951.
38. Mole, R. H.: Fibrinolysin and the fluidity of the blood post mortem. J. Path. & Bact., 60:413, 1948.
39. Moon, Henry D., and Rinehart, James F.: Histogenesis of coronary arteriosclerosis. Circulation, 6:481, 1952.
40. Muirhead, E. E., and Montgomery, P. O'B.: Thromboembolic pulmonary arteritis and vascular sclerosis: Its experimental production in rabbits by means of intravenously injected human amniotic fluid and autogenous blood clots. Arch. Path., 52:505, 1951.
41. McKeown, F.: The pathology of pulmonary heart disease. Brit. Heart J., 14:25, 1952.
42. McLetchie, N. G. B.: The pathogenesis of atheroma. Am. J. Path., 280:413, 1952.
43. Papacharalampous, Von N., and Zollinger, H. U.: Morphologie und Pathogenese des subtotalen und totalen Coronarverschlusses (Intramurales Hämaton, Thrombose, Arteriosklerose, Coronaritis). Schweiz. Med. Wchnschr., 37:859, 1953.
44. Paterson, J. C.; Slinger, S. J., and Cartley, K. M.: Experimental coronary sclerosis. I. Medial degeneration as the primary lesion in coronary sclerosis of cockerels. Arch. Path., 45:306, 1948.
45. Paterson, J. C.: Factors in the production of coronary artery disease. Circulation, 6:732, 1952.
46. Rinehart, James F., and Greenberg, Louis D.: Pathogenesis of experimental arteriosclerosis in pyridoxine deficiency. Arch. Path., 51:12, 1951.
47. Rotter, W.: Über die Bedeutung der Ernährungsstörung, insbesondere des Sauerstoffmangels für die Pathogenese der Gefässwandveränderungen mit besonderer Berücksichtigung der "Endarteritis obliterans" und der "Arteriosklerose." Zugleich ein Beitrag zum Entzündungsproblem. Beitr. z. path. Anat. u. z. Allg. Path., 110:46, 1949.
48. Saphir, O.: Bands and ridges in the pulmonary artery. Arch. Path., 14:10, 1932.
49. Saphir, O.: The fate of carcinoma emboli in the lung. Am. J. Path., 23:245, 1947.
50. Saphir, Otto, and Gore, Ira: Evidence for an inflammatory basis of coronary arteriosclerosis in the young. Arch. Path., 49:418, 1950.
51. Schlichter, J. G.: Experimental medionecrosis of the aorta. Arch. Path., 42:182, 1946.
52. Schlichter, J. G.: Vascularization of the aorta in different species in health and disease. Am. Heart J., 35:850, 1948.
53. Schlichter, J. G.; Katz, L. N., and Meyer, J.: The occurrence of atheromatous lesions after cauterization of the aorta followed by cholesterol administration. Am. J. M. Sc., 218:603, 1949.
54. Schneider, Charles L.: Complications of late pregnancy in rabbits induced by experimental placental trauma. Surg., Gynec. & Obst., 90:613, 1950.
55. Schneider, Charles L.: "Fibrin embolism" (disseminated intravascular coagulation) with defibrination as one of the end results during placenta abruptio. Surg., Gynec. & Obst., 92:27, 1951.
56. Shore, M. L., Zilversmit, D. B., and Ackerman, R. F.: Aortic synthesis of phospholipids in experimental rabbit atheromatosis. Circulation, 9:594, 1954.
57. Ssolowjew, A.: Experimentelle Untersuchungen über die chromatrope Grundsubstanz der Arterienwand. Virchows Arch. f. Path. Anat., 261:253, 1926.
58. Ssolowjew, A.: Experimentelle Untersuchungen über die Bedeutung von lokaler Schädigung für die Lipoidablagerung in der Arterienwand. Ztschr. ges. exper. Med., 69:94, 1930.
59. Stress, fibrinolysis, and atheroma. Brit. Med. J., 2:1343, 1949.
60. Taylor, H. E.: The role of mucopolysaccharides in the pathogenesis of intimal fibrosis and atherosclerosis of the human aorta. Am. J. Path., 29:871, 1953.
61. Wagner, Von Hugo: Über rhythmische Strukturen und thrombotische Auflagerungen der Aortenintima. Ein Beitrag zur Morphogenese der diffusen Intimaverdickung und des arteriosklerotischen Polstera. Schweiz. Ztschr. Allg. Path., 17:258, 1954.
62. Wartman, W. B.: Vascularization and haemorrhage in the arterial wall. "Studies in Pathology" presented to Peter MacCallum. Melbourne: University Press, 1950.
63. Wartman, W. B., Jennings, R. B. and Hudson, B.: Experimental arterial disease. I. The reaction of the pulmonary artery to minute emboli of blood clot. Circulation, 4:747, 1951.
64. Wartman, W. B., Hudson, B. and Jennings, R. B.: Experimental arterial disease. II. The reaction of pulmonary artery to emboli of filter paper fibers. Circulation, 4:756, 1951.
65. Waters, L. L.: Studies on the mechanisms of vascular disease. Mississippi Doctor, 25:380, 1948.
66. Winternitz, M. D., Thomas, R. M. and LeCompte, P. M:. The Biology of Arteriosclerosis. Springfield, Illinois: Charles C Thomas, 1938.
67. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P.; Geisler, M. A., and Wilcox, B. B. Coronary artery disease in men 18-39 years of age. Am. Heart J., 36:683, 1948.

Atherosclerosis

The Atherosclerosis Problem

LOUIS N. KATZ
Chicago, Illinois

ATHEROSCLEROSIS is the hub of the arteriosclerosis problem. Once it is conquered, a tremendous dent in morbidity and mortality rates will follow, and the average life span will be greatly lengthened. Are we making progress? I think we are. Evidence for this has been or will be presented during this conference.

Let us see wherein this progress lies. It lies first of all in the rejection of the view that atherosclerosis is merely aging which is inevitable and irreversible, and, more important, it lies in the acceptance, instead, that it is a disease which is reversible and, we are convinced, preventable. Basically it is a metabolic disorder involving lipid-cholesterol-lipoprotein metabolism. The theory upon which the work of the Michael Reese group* is now based considers that, when dealing with population groups, altered lipid-cholesterol-lipoprotein metabolism is engendered by a luxus of calories, lipid and cholesterol in the diet over the life span. This acquired rich and unbalanced diet, particularly in the sedentary, with its high fat content (constituting up to 50 per cent or more of the caloric intake) influences the metabolism of lipid-cholesterol-lipoprotein and so sets the background for the ready genesis of atherosclerosis in the population. Dietary deficiencies of some vitamins and amino acids may act to accelerate atherogenesis. Certain diseases, habits, stresses, genetic traits and local factors (such as vascular trauma and vascular infections) may act as triggers of this process in individual cases. Hypertension too is an accelerator of atherosclerosis. But basic to all of these triggers and accelerators, in most cases at least, is the dietary pattern over the life span, consisting of an excess of calories, lipid and cholesterol.** In the last few years the evidence in support of this theory has been summarized by my associates and myself (see Bibliography).

On this basis further studies must be directed along three principal lines, namely: (1) clinico-pathological, (2) epidemiological and (3) experimental. From the first two we obtain the background of atherosclerosis. The clinico-pathological and epidemiological studies pose the problems to be tested. In the experimental studies we put questions derived in this way and seek to obtain answers concerning etiology, pathogenesis, treatment and prophylaxis. After detailed analysis and adequate confirmation in the animal, we are prepared to verify our concepts of treatment and prophylaxis by cautious probes in man. This has been the modus operandi of the work of our group in the last two decades. It is my considered judgment that only by such a broad perspective can the problem of atherosclerosis be conquered. This approach plus care in designing the research program and care in interpreting its results will avoid fruitless — as contrasted with useful — bickering and "theorizing" ("idle speculation") which divert so much energy from the primary task of filling in gaps in our knowledge.

The problem of atherosclerosis brings together investigators from many disciplines and points up the trend toward narrow specialization which has crept into medical science recently. Appreciation of the views of persons from other disciplines working on atherosclerosis and understanding of the methodologies and "jargon" of the multiplicity of disciplines essential for understanding atherosclerosis will go as far as

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

*The group consists at present of Drs. R. Pick, J. Stamler and myself and a number of dedicated technicians. In the past it included Drs. D. Dauber, L. Horlick and S. Rodbard.

**There is no doubt that atherosclerosis develops more readily in certain abnormal blood vessels than in normal ones, but we hold the view that it depends here too on the character of the lipid-cholesterol-lipoprotein metabolism.

any single ordinary discovery in accelerating our conquest of this disease. It definitely points up the need of overcoming the defects inherent in excessive specialization without loss of its benefits. Group research is one answer; a group which combines many talents can accomplish much, when supplemented by brilliant individualistic effort. Who amongst us knows which bit of knowledge, or, more likely, which combination from many disciplines will unlock the closets where the solutions of atherosclerosis are hidden? It follows, therefore, that we desperately need a meeting of minds, a return to broader perspectives in science, a counterbalance to the trend to specialization in research.

Clinico-pathological studies had a dominant role in atherosclerosis for many years. They helped define the correlation of this vascular disorder with the diseases affecting man. Morphological pathology has been useful in this regard when it recognized that its examination revealed only the anatomical character of this vascular process. From the anatomical examination one can only conjecture the dynamic biochemical, biophysical and physiological processes, which over the lifetime of the deceased led to the necropsy findings. The findings at autopsy must not be mistaken for the living process.

Clinical studies have been useful too in outlining the manifestations and sequelae of atherosclerosis, as well as the circumstances under which they become apparent. A moment's reflection will convince one that there is a vast domain of subclinical atherosclerosis that cannot now be definitely revealed by present methods of clinical study. Clinical manifestations and sequelae must not be confused with the disease itself, and procedures affecting the former must not be wrongly interpreted as necessarily reflecting effects upon the basic pathogenesis of the disease itself. The value of alleviating detrimental manifestations and of avoiding unwanted sequelae is obvious, but this does not necessarily mean getting to the bottom of the problem. Tests, even elaborate ones, and the factors altering the tests, do not necessarily reveal the pathogenesis, treatment or prophylaxis of the disease process itself. It is not from the manifestations nor from the sequelae that the answers will come, but only from an understanding of the total organism in its environment, on the one hand, and the biological process in living cells, on the other. And, by the way, it is necessary to remind oneself constantly, over and over again, that changes in the blood do not always reflect the changes occurring within the living cells nor the adaptations of the entire organism.

A great deal of information is obtainable from the study of man in his natural environment by methods which have proven so effective in the infectious and contagious diseases and which have been fruitful in the science of ecology as far as plants, and animals below man, are concerned. Man is of different ethnic origins, of two sexes, and of various ages. In the world today, and even in the U. S. A., man's environment is extremely variable as regards to climate, occupation, mores, diet and other stresses. This too is true of earlier periods of man's existence. Some of this data can be procured from available archeological and anthropological studies. More can be gotten, from vital statistics, especially in recent years, death certificates and census figures. Field studies need to be developed. A concerted attack in an expanding amount needs to be developed to pluck out the information buried in these rich sources of data. This will depend on correlations of differences obtained. By going from the study of the individual to that of large groups and by using the statistical approach based on probabilities, we may be able to derive as exact mathematical leads to the factors resulting in atherosclerosis, as is derived by the physicist and chemist when dealing with populations of molecules in different environments. Of course, epidemiology applied to atherosclerosis is a young and virgin field. But it is vigorous and already has made important contributions. The information available has pitfalls for the unwary. But with time, diligence and skill, these can be recognized and discounted. Concentration by properly trained scientists in this underdeveloped discipline should change the trickle to a veritable bonanza of new, needed, vital information from which questions can be put to the experimentalists to get answers from their animal studies.

The greatest impetus to the problem of atherosclerosis has come recently from the experimental approach in the animal laboratory. This is because of three fundamental advantages of this type of approach, namely:

1. The experiment can be designed to answer specific questions.

2. Controls can be run to exclude extraneous influences, and by using large enough samples and by random selection of "aliquots," statistically significant changes can be distinguished from sampling errors.

3. The lesions of atherosclerosis themselves can be studied in all its stages rather than some secondary manifestation or sequelae, or a presumed associated index.

It goes without saying that experiments must be properly conceived and executed. A mass of information can come from properly conducted animal experiments concerning: (1) the role of dietary and other ingested materials, (2) the effect of various microorganisms resident in the gastrointestinal tract, (3) the influence of hormones and other humoral and neurogenic regulators of bodily function, (4) the intermediary metabolism of lipid, cholesterol and phospholipids, their kinetics, energetics and enzymology, (5) the biology and metabolism of the blood vessels, (6) the transport of fatty substances in the blood and tissues, et cetera. Much information has already been gained but many gaps remain and new problems have arisen as old ones were solved. Thus, the revelation of differences in biological response of different arterial beds—as for example between the coronary arteries and the aorta—has posed the problem of the cause of this difference.

Many findings in man, especially as to sex, have been confirmed and analyzed in animals and new insight into its mechanism obtained. The role of age and species differences has received growing attention. Some therapeutic and prophylactic potentialities have been revealed so that some investigators may feel that animal experimentation has all the answers to atherosclerosis. Far from it. The mere fact that species differences do exist demand that all animal observations of significance must be reexamined in the species we are interested in, man. Otherwise ghosts may be created which fade in the piercing light of clinical experience.

Obviously, crystallization of the previous information concerning atherosclerosis will come only by the proper free interplay and adequate fusion of the three major approaches to the problem, epidemiological, clinical and experimental. We are getting to our goal—but we have not reached it yet. We have a motif, the life span unbalanced luxus diet, rich in calories, fats and cholesterol. We must look into other aspects, as for example: (1) the causes for localization of lesions in particular sites, (2) the causes for intimal ulceration, (3) the influence of hemorrhage and thrombosis, (4) the influence of physical and physical stresses. These are, as it were, decorations to beautify the motif, they must not be mistaken for the motif itself.

We have come a long way along the road to the solution of the problem of atherosclerosis in the last two decades. The goal is dimly glimpsed through the haze ahead. But we are not there yet, considerable labor on the part of many, carried out in a truly scientific atmosphere still lies ahead. But the reward will more than repay the effort still to be employed.

Bibliography

Katz, L. N., and Stamler, J.: Experimental Atherosclerosis. Springfield, Illinois: Charles C Thomas, 1953.

Stamler, J.; Katz, L. N., and Pick, R.: Nutritional-endocrinological interrelationships in the pathogenesis of hypertension and atherosclerosis over the life span. Fourth Annual Report on Stress. Selye and Heuser, eds., p. 245. Montreal, Canada: Acta, 1954.

Katz, L. N.; Pick, R., and Stamler, J.: Atheroclerosis. Modern Concepts, 23:239, 1954.

Katz, L. N.; Stamler, J., and Pick, R.: The role of hormones in atherosclerosis. Symposium on Atherosclerosis, National Academy of Sciences, National Research Council, Washington, D. C., 1954. N.A.S.-N.R.C. Publication, 338:236, 1954.

Stamler, J.: Basic research on atheroclerosis. Proc. Am. Pharmaceutical Mfg. Assoc., p. 34, 1955.

Stamler, J.; Katz, L. N.; Pick, R., and Rodbard, S.: Dietary and hormonal factors in experimental atherogenesis and blood pressure regulation. Recent Progress in Hormone Research. 10:401, 1955.

Katz, L. N.: The role of diet and hormones in the prevention of myocardial infarction. Ann. Int. Med. (in press).

If one were to use as criteria the amount of life spoiled by disease, instead of measuring only that destroyed by death; or the number of days lost from pleasure and work because of so-called minor ailments; or merely the sums paid for drugs, hospitals, and doctors' bills, the toll exacted by microbial pathogens would seem very large indeed. Microbial diseases have not been conquered. Rather, scientists have resigned themselves to the belief that a relative protection against them can be had only at the cost of a huge ransom.—RENE J. DUBOS, Ph.D., *Journal of the American Medical Association*, April 23, 1955.

Mode of Life and the Prevalence of Coronary Heart Disease

ANCEL KEYS
Minneapolis, Minnesota

IT IS generally agreed that neither infection nor external physical trauma can be blamed for any appreciable primary role in the development of the great majority of cases of atherosclerosis and coronary heart disease. Moreover, we have fortunately abandoned the view that aging, *per se*, is responsible. Finally, there is abundant proof that individuals and whole populations differ greatly in this tendency to develop the basic, primary lesions and the resulting consequences.

Accordingly, the responsible factor or factors must be sought for either in heredity or in the mode of life, or in both. I shall discuss heredity shortly and may persuade you that even though heredity influences the outlook for some people, most of us are *not* doomed simply because of the genes we have inherited. But we still must ask, "What kind of people develop coronary heart disease?"

The popular picture of the coronary heart disease victim is that of a burly business or professional man, fat and soft from overeating and lack of exercise, who smokes and drinks too much because he is tense with the stresses of modern life in his effort to get to the top. Obviously he is a white, urban American and very likely in his family tree there are forebears who died suddenly.

Perhaps there is something in this description but as a totality it is a caricature. Such men do exist and some of them die of coronary heart disease. But many men of this type escape and the great majority of coronary victims are not so readily pigeonholed as to type. The diversity is apparent from a survey of patients in a few general hospitals.

In a recent spot check of all patients in the medical sections of five hospitals in the Twin Cities we found eighty-two patients with coronary heart disease. Among these less than a third were or had been obese, 42 per cent were women, and among the men many were non-smokers and only a minority were in the business or professional class. Obviously, the problem is complicated.

There is a host of reasons to insist that the mode of life must be important and, I think, dominant. But what factors in the mode of life can be singled out for suspicion or for outright blame?

Besides heredity *per se*, let us list the characteristics of people that may deserve consideration. These include the habits of diet (both quantity and character), of physical activity, of emotion and of drinking, of smoking and of sex indulgence, all of which, theoretically, could be changed if need be. To these may be added sex itself and the body build, meaning the skeletal type, neither of which can be considered an expression of the mode of life though both merit a comment in passing.

Sex

In populations with much coronary heart disease, as in the United States, the mortality from this cause at relatively young ages is much higher in men than in women, and we say that females are protected because of their sex hormones. Actually, females are by no means immune. In 1952, 4,862 American women under fifty are recorded as dying of coronary heart disease and "myocardial degeneration." Nor do they rapidly lose their relative protection as soon as they reach the menopause. The female death rate from coronary heart disease does not equal that of the male until after the age of eighty years.

All of this is in the U.S. in populations where coronary heart disease is less common than here,

From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minnesota.
Some of the data cited here were obtained with the help of grants-in-aid from the American Heart Association, the Minnesota Heart Association, the National Dairy Council, the American Dairy Association, and the U. S. Public Health Service (grant No. H 10, recommended by the Cardiovascular Study Section).
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

TABLE I.

Mortality ascribed to arteriosclerotic heart disease in Italy (1950) and among Whites in U.S. (1952). Rates per 100,000, by sex.

	50-54 years			55-59 years		
	M	F	M/F	M	F	M/F
U.S.	544.1	183.8	2.96	877.9	331.0	2.65
Italy	117.1	51.6	2.27	187.3	107.9	1.74
U.S./Italy	4.65	3.56	—	4.69	3.07	—

the sex ratio of coronary heart disease is also less than here, as indicated in Table I.

These are vital statistics. The general accuracy of the picture they present has been checked by several methods—consultation with many physicians, surveys of many hospitals, coroners' reports, the experience of insurance companies in the two countries and by detailed analysis of the statistics.

There are only two possibilities to explain the facts. Either Americans tend to have a remarkably bad heredity in this respect or there is something in our mode of life that promotes the deposition of cholesterol and the formation of thrombi in our coronary arteries. And this detrimental influence is prominent among our men but our women are also affected.

Body Build or Type

It has been reported that overweight is not important but that men of stocky or heavy muscular, "mesomorphic" build tend to have coronary heart disease at an early age (Garn et al, 1951; Gertler, White, et al, 1954). If this is so, some of the trait may be hereditary, but we may ask whether the mode of life in childhood—the diet and habits of exercise, for example—influences the eventual skeletal type. And we can still insist that body build cannot be a dominant factor because there are plenty of mesomorphs in populations, like the Italians and Bantu, who suffer far less coronary heart disease than we do. In other words, the body build may be partly an expression of the mode of life and in any case it is certainly not fatal in itself.

Race and Heredity

It is easy to fall back on "race" and "heredity" as explanations for the obvious differences between individuals and between populations in their susceptibility to arteriosclerotic heart disease. Several excellent studies (e.g., Boissevain, 1931; Boas et al, 1948; Wilkinson, 1950; Adlersberg et al, 1950), have painstakingly traced many members of a number of unfortunate kindreds in which coronary heart disease is prominent, cutaneous xanthomata are not rare and high blood cholesterol values tend to be the rule. Citation of these cases as indicating a genetic basis for our number one cause of death is gratifying to the professional ego of the geneticist and absolves the medical researcher from any pressure to find out why people and populations differ. A few generations ago the attempt to learn how to prevent tuberculosis could have been opposed on equally meretricious facts and argument.

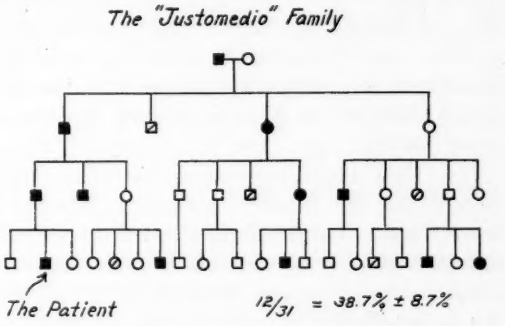


Fig. 1. Family tree of the "Justomedio" family. Squares represent males, circles females. Members dead of coronary heart disease are indicated in solid black. The symbols with a diagonal line indicate persons who died in youth.

It should be noted that the discovery of any family which apparently is coronary-prone is always good for at least a paper or two in the medical literature. This fact is eloquent testimony to the rarity of cases where peculiar heredity seems to be the basic cause of the trouble. Moreover, the freqency of coronary heart disease in our general population is so high that one may question how much of the coronary heart disease in so-called coronary families actually represents a great excess beyond ordinary expectations.

Consider the family tree, covering four generations, given in Figure 1. The physician called to attend a man in his forties dying of coronary heart disease is impressed to discover that the patient's father and an uncle died of coronary heart disease. When the family is traced further it appears that the patient's grandfather was found dead in bed one morning and that his

great grandfather also died suddenly. The upshot is that among thirty-one descendants of the suspect great grandfather, excluding five who died in youth, there is good reason to label twelve dead of coronary heart disease, or a possible incidence of 38.7 per cent.

This is impressive indeed. Or is it? We find that the standard error of this incidence value is ±8.7 per cent and that for the U.S. white population as a whole the vital statistics show that nearly 30 per cent of all deaths beyond youth are ascribable to coronary heart disease.

The family illustrated in Figure 1, in fact, does not deviate significantly from our national picture. The "Justomedio" family is fictitious. This chart was devised to illustrate our *national* plight and not that of a particularly coronary-prone family.

Now these critical remarks are not to be taken as a denial that heredity operates in coronary heart disease. Unquestionably a serious abnormality in cholesterol metabolism or of vascular architecture leading to coronary heart disease *can* be inherited. But I am unaware of any evidence to show that this is anything more than a rare occurrence. It recalls the *one* case of fatal coronary occlusion found in a large series of autopsies on Bantu natives in Johannesburg. The victim was a twenty-three-year old girl! Very probably she suffered from a "metabolic fault" and it might even have been hereditary.

A stronger case can be made for the existence of familial tendencies, as opposed to strict inheritance, towards more or less coronary heart disease. But for these it is enough to cite the influence of a common mode of life imposed by family custom in food, activity, and so on.

Objection may be made that we still must credit racial genetic inheritance as a *possible* explanation of the difference in coronary proneness between people in the United States and those in Japan or the Bantu or even in Italy. In opposition are the following points.

1. Such information as we have indicates that American Negroes, unlike the Bantu, are by no means immune. Dr. Jeremiah Stamler has recently obtained evidence, confirmatory of other findings, indicating that Negro men in Chicago have an age specific mortality from arteriosclerotic heart disease at least as high as white men in Chicago. If it is argued that the American Negro has much other negroid blood besides Bantu, it must be pointed out that the general picture of the absence of coronary heart disease among the Bantu seems to prevail among all of the negroid people of Africa who furnished the slaves brought to the United States.

2. Larsen (1955) finds that the incidence of severe atherosclerosis and coronary heart disease among the semi-Americanized Japanese in Hawaii is lower than that of white Hawaiians but it is much higher than found in Japan.

3. Physicians anywhere in the United States who have many Americans of Italian descent among their patients will testify that coronary heart disease is far from a rarity among these people. In selected samples of Americanized Italians and Jews in New York, Epstein and Boas (1955) found no difference in the incidence of atherosclerosis among the men but evidence for coronary heart disease was more frequently seen among the Jewish men, but not among the Jewish women, than among the Italo-Americans. The Jews and Italo-Americans did not differ in the incidence of either hypertension or diabetes.

4. Within Italy there are great differences in the prevalence of coronary heart disease which are readily explicable, not by race, but by the customary local diets.

5. The experiences of the World War and after have shown that among Nordic and Teutonic peoples, too, coronary heart disease can decline greatly in spite of their race if they change their manner of life, particularly their diets.

To these points may be added other bits of information that may be relevant. In studies on population samples we have repeatedly found that at equal age, both the serum cholesterol concentration and the mortality rate from coronary heart disease are much higher in the United States, England and Sweden than in various parts of Italy and Spain. We believe that dietary differences are adequate to account for this, but the question may be asked whether it is possible that Nordics or Anglo-Saxon-Teutonic peoples have a genetic tendency to higher cholesterol than the Latin or Mediterranean peoples.

Firstly, it may be replied that within the Spanish and Italian populations, at least, there are differences in serum cholesterol and coro-

TABLE II.

Serum total cholesterol concentration, in mg. per 100 ml., in clinically healthy, middle-aged businessmen in Minnesota, classed as to eye color and matched as to relative obesity and age.

Eye Color	No. of Men	Serum Cholesterol	
		Mean	S.E.
Blue	70	251.8	±5.2
Brown	48	257.8	±5.4

nary heart disease prevalence that are explicable by dietary but not by racial differences (cf. Keys, 1952, 1953, 1954; Keys et al, 1954, 1955).

Secondly, we have attempted to approach a classification of Minnesota men into the more "Nordic" and the more "Mediterranean" types by eye color, men with clear blue eyes being considered to be more Nordic than those with deep brown eyes. Table II summarizes the serum cholesterol values in these two groups, matched in age and in relative obesity. The *brown* eyed men tend to have higher serum cholesterol values but the difference between them and the blue eyed men is not statistically significant.

Far more research is needed to show how much or how little of our tremendous incidence of coronary heart disease depends upon heredity. A few people are working on the question but all signs point to heredity as being only a minor factor and, moreover, one that can be overcome. I insist as forcibly as I can that our research effort must be geared to the proposition that heredity will not prevent success in the prevention of coronary heart disease.

Overweight and Obesity

Following the lead of life insurance companies, it has been widely believed in this country that a high frequency of overweight and obesity in the American population explains to a considerable degree the high frequency of coronary heart disease in the United States.

Elsewhere I have pointed out some of the most serious questions about the insurance company data used to support this thesis (Keys, 1954, 1955). While there will be little dissent from the opinion that extreme obesity is a health hazard in general, and perhaps for heart disease in particular, the evidence from various sources is far from convincing about coronary heart disease. Among other things, we may ask whether insurance applicants are a truly repre-

TABLE III.

Frequency of overweight among clinically healthy men 20-60 years old. Values listed are percentages of the men in the samples studied who were 10 per cent or more and 20 per cent or more heavier than the average for height and age given in the U.S. Medico-Actuarial tables. "Police-Fire" are men in the city fire and police departments.

Occupation	Region	Overweight By	
		10%	20%
Sedentary Work	Naples, Italy	28.1	10.3
Sedentary Work	Bologna, Italy	40.0	21.8
Sedentary Work	Malmö, Sweden	13.9	3.7
Sedentary Work	Twin Cities, Minnesota	22.5	5.3
Police-Fire	Naples, Italy	29.4	9.4
Police-Fire	Bologna, Italy	32.1	19.5
Police-Fire	Malmö, Sweden	21.4	10.0
Police-Fire	Twin Cities, Minnesota	42.0	18.0
Heavy Work	Naples, Italy	16.2	6.3
Heavy Work	Malmö, Sweden	14.0	4.3

sentative sample of overweight persons. In any case only a small fraction of our total burden of coronary heart disease could possibly be ascribed simply to overweight or obesity.

At most it might be claimed that grossly overweight men in the U.S. have a mortality rate from coronary heart disease at relatively early age some 50 per cent higher than the general population of men who are not so obese. The question then turns on the proportion of the population that is grossly overweight. The insurance companies have selected 20 per cent over the "standard" average body weight for given height and age as the point beyond which they attach a penalty. One estimate, from the Metropolitan Life Insurance Company, is that perhaps 7 per cent of American men are in this category though the proportion among insurance applicants is smaller than this. It is easy to calculate then, that over 95 per cent of the coronary heart disease mortality among American men occurs in persons who are not obese enough to be specially "rated" by the insurance industry.

Moreover, in all studies so far reported on actual coronary patients the distribution of relative body weight among these patients proves to be similar to that of the rest of the population of the same age who do *not* have coronary heart disease (cf. Keys, 1954, 1955).

Finally, let us ask whether the lower incidence of coronary heart disease in some other populations can be explained by the absence of overweight persons in those populations. Actually, "overweight" occurs in all countries and even among such special groups as Bantu in South Africa overweight is not rare. But for the present

TABLE IV.

The distinction between obesity and relative overweight as illustrated by four men, all of the same height and age.

Body Weight lbs.	% of Weight in		Obese	Overweight
	Fat	Muscle		
160	20	50	No	No
160	30	40	Yes	No
180	20	50	No	Yes
180	30	40	Yes	Yes

purpose some of the most useful data are from recent surveys in Italy and in Sweden as summarized in Table III. "Overweight" was calculated from the ordinary U.S. Medico-Actuarial Tables of weight for height and age.

It is obvious that Americans have no monopoly on overweight. Among sedentary men the Italians sampled in Naples and in Bologna exceed Minnesotans as well as southern Swedes in this regard. Many members of the Police and Fire Departments in all of the cities are overweight, but Minneapolis and Bologna are neck-and-neck for overweight top honors. Finally, it will be noted that the heavy workers of Naples tend to be overweight more often than their counterparts in Malmö.

Dr. Brock may choose to say something about overweight among the Bantu and Cape Coloured men in South Africa. But it may be permissible here for me to cite some figures Dr. Bronte Stewart and I obtained last spring when we were working in Dr. Brock's laboratory. Among the first 90 Cape Coloured men we studied, 16 were 10 per cent or more overweight and 6 were more than 20 per cent overweight. Among the first 119 Bantu we studied, 13 were 10 per cent or more overweight and 6 were more than 20 per cent overweight. One of these Bantu was 5 feet 8 inches tall and weighed over 260 pounds.

These data certainly do not suggest that overweight is a primary factor in the development of coronary heart disease. For there is no doubt that the relative prevalence of coronary heart disease is very different in these populations, with Minneapolis at the high end and the Bantu at the bottom. Bologna is above Naples but far below Malmö in the prevalence of coronary heart disease. And I suppose that the frequency of coronary heart disease among the Cape Coloured men is somewhere between the values for Naples and Bologna.

Nothing of what I have said should be taken to mean that overweight is of no importance or that we should stop condemning obesity. Gross obesity, like any other marked departure from the central tendency of mankind, is undesirable and may be unhealthy too. But in regard to coronary heart disease, it seems impossible to assign to it more than some aggravating or accelerating influence to a process, that is to atherosclerosis, that is primarly conditioned by other factors.

It may even be that obesity, *per se*, has no influence but that in some populations men who are obese also tend to have other characteristics that lead to trouble. They may, for example, indulge in high fat diets as well as merely eating a lot. And, if we credit lack of exercise as having a real influence, it is significant to note that most fat men tend to move slowly and infrequently. In any case there is no reason to believe at present that the American problem of coronary heart disease will be solved, or even reduced much, by "curing" our obesity.

One final word on this subject, now that I have seemingly used the terms obesity and overweight interchangeably. Actually, obesity means fatness and it is only at the extremes that fatness and overweight tend to be closely related. We may ask our insurance friends how they would predict the prospects for coronary heart disease for the four men in Table IV.

These men are all of the same age and height. Their fatness is indicated as the percentage of their body weight made up of fat. Two men are obese but only one of these is overweight. Two men are overweight but only one of these is obese. The point is that neither insurance nor any other data on coronary heart disease have made this distinction, and all of the data that purport to show excessive mortality among fat people actually refer only to relative body weight.

Smoking

The reports by Hammond and Horns (1954) and by Doll and Hill (1954) on the mortality experience of men of known smoking habits have greatly increased interest in the theory that smoking may produce or promote coronary heart disease. In spite of the absence of concrete evidence, or a plausible theory, of mechanism for a true cause-and-effect relationship, it is not easy to disregard the finding that the death rate ascribed to coronary heart disease is

50 to 100 per cent greater among the smokers than among the non-smokers in the large population samples studied.

Berkson (1955) has severely criticized statistical shortcomings in these studies, arguing that the reported association between coronary heart disease and the habit of smoking could be spurious. Extreme assumptions about bias in the selection of the participants in the studies are required to defend this ultra-skepticism. In any case, it is useful, temporarily, to accept the facts as they appear and to proceed further to inquire what they may mean. The findings as they stand would be consistent with any one of three hypotheses:

1. Smoking, directly or indirectly, causes coronary heart disease, which means that smoking *per se* promotes atherosclerosis and/or thrombosis in the coronary arteries.

2. Smoking is a secondary aggravating factor in the presence of primary forces tending to produce atherosclerosis and/or thrombosis.

3. Smoking *per se* has no influence but the smoking habit is favored by men who, because of heredity and/or mode of life in other respects, are unusually prone to coronary heart disease.

I believe there is already evidence at hand to disprove the hypothesis that smoking has an important primary effect in the development of coronary heart disease. At least we can show that great differences in the prevalence and mortality of coronary heart disease in different populations are quite independent from any differences in the prevalence of smoking.

Over a great part of the world the majority of the men smoke cigarettes. In poorer countries fewer cigarettes are smoked but they are more completely smoked. In terms of nicotine and irritant received, the net effect of smoking ten cigarettes to the last millimeter may be greater than smoking twenty cigarettes in the manner common in the United States.

In Italy we have found by personal surveys that 40 to over 70 per cent of the men are smokers, as shown in Table V. From one-fourth to over half of all men studied were found to smoke from ten to fifty cigarettes daily and the habit had been established in youth. Even among Sardinian shepherds and coal miners, whose occupations and economic circumstances tend to discourage smoking, at least 20 per cent of the men were heavy smokers.

TABLE V.

Percentage of men under 60 years of age in various populations who smoke more than 10 cigarettes daily or more than 0.5 pound of pipe tobacco per month.

Twin Cities, Minnesota, Business Men	52%
Bologna, Italy, Employees	68
Cagliari, Sardinia, Employees	73
Sardinia, Coal Miners	63
Sardinia, Shepherds	43
Nicotera, Italy	63
Cape Town, Europeans	72
Cape Town, Coloured	81
Cape Town, Bantu*	72
U.S.A. Surveys, ages 50-59	53

*Mostly pipe smokers

Obviously, in regard to smoking, there is no great difference between men in the United States and men in Italy, or between men in southern Italy and those in Bologna. But, as has been noted, these areas differ greatly in the prevalence of coronary heart disease.

Even greater differences in coronary disease prevalence are found within populations in Cape Province, South Africa, but again, as shown in the table, there is no corresponding difference in the custom of smoking. The Bantu, at the bottom of a steep economic ladder, can rarely afford to be a heavy cigarette smoker, but over half of them in our sample smoke, in pipes, at least half a pound of tobacco a month. And in these men coronary heart disease is extremely rare. The Cape Coloured man, whose tendency towards coronary heart disease is certainly greater than the Bantu but is far less than that of the local European, is similar to the local European in his smoking habit. More often than not, the Cape Coloured man is a heavy smoker of cigarettes.

In Japan, too, heavy cigarette smoking is common but the data of Kimura (1955) confirm the long-standing opinion that coronary heart disease and severe coronary atherosclerosis are very uncommon among Japanese men in Japan.

These data do not, of course, answer all of the questions about the effects of smoking. It is possible to suggest that if the Bantu or Japanese or the southern Italian did not smoke they might be even freer of coronary heart disease. But it is not possible to deny that some factor other than smoking must be the dominant reason for the high incidence of coronary heart disease in the United States and other high coronary countries.

A trial calculation is informative. Suppose we

accept the most optimistic interpretation of the Hammond and Horns data and assume that if our American men stopped smoking they would experience only the coronary mortality observed among the non-smokers in the Cancer Society study. In other words, for roughly half of our men in the fifties the mortality from coronary heart disease would be reduced by about 40 per cent. The total coronary mortality rate for all of the men in the fifties would be reduced, then, by some 20 per cent and this is certainly not negligible. But to equal the Italians' experience, *including* the 50 per cent or more of them who are smokers, we should have to effect three to four times this reduction!

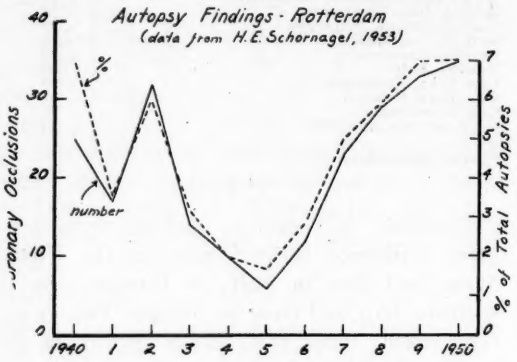


Fig. 2. Number of coronary occlusions, and percentage of total autopsies represented by them, in the Municipal Hospital records at Rotterdam, the Netherlands, for the years 1940 to 1950. Data from Schornagel, 1953.

There is as yet no evidence at all that stopping smoking would have *any* effect on our current or future burden of coronary heart disease. But, as indicated above, the best result we could hope for would still leave us with a greatly excessive mortality.

It has been suggested that the great decrease in smoking in some European countries during the war might have been influential in producing the sharp declines in coronary heart disease seen in those countries at the time. But, as pointed out by Schornagel (1953) for the Netherlands, this theory cannot be defended by a critical analysis of the data. In the Netherlands the wartime decline in coronary heart disease, and the post-war rise, affected both men and women equally but only a negligible proportion of the women in the Netherlands smoked before, during or after the war. Further, in Denmark the wartime decrease in smoking was the same as in other parts of Northern Europe but there was no decline in coronary heart disease in that country during the war. But it should be noted that the Danish *diet* was not changed during the war.

Alcohol

Relative rarity of severe atherosclerosis and coronary heart disease among alcoholics has been commented on occasionally in the literature. In Japan, Kimura (1955) observed marked atherosclerosis at autopsy more frequently among men who habitually drank *and* smoked cigarettes than among men of the same age who indulged in neither. Among elderly men in Britain, the average serum cholesterol concentration was considerably lower among the heavy drinkers than among abstainers and moderate drinkers (Hobson et al, 1953). Finally, it has come to be a common custom of competent cardiologists, presumably justified by clinical experience, to permit, or even to advise, their coronary patients to use alcohol but, of course, in moderation.

The evidence on alcohol is not great but it seems safe to conclude that the use of alcohol does not promote either atherosclerosis or coronary heart disease.

Physical Activity

It is widely believed, and some impressive evidence can be cited in support, that men whose occupations involve physical work are less prone to coronary heart disease than are sedentary men. But the best evidence is from countries such as England and Sweden where the distinction between manual and physical work is greater than in the United States and where other differences in the mode of life are more obviously associated (Hedley, 1939; Morris and Heady, 1953; Morris *et al*, 1953; Biörck *et al*, 1954).

In the United States these distinctions between manual and mental labor are disappearing. Our mental workers are not apparently doing more manual work but our manual workers are required to exert less and less physical effort to do their jobs. Perhaps this is why it is more difficult in this country to demonstrate the major differences between classes of workers in regard to the incidence of coronary heart disease. Or is it because we are also more homogeneous in regard to income, diet and general mode of life?

For instead of physical activity as the criterion, in many countries a social or economic classification would show differences in the prevalence of coronary heart disease at least as great as can be demonstrated when men are classed according to physical activity. Malhotra's (1951) data from India, summarized in Table VI, are typical.

Morris (1955), has recognized the serious analytical problem resulting from the fact of high intercorrelation between a number of factors in the mode of life that may singly or together promote atherogenesis and coronary heart disease. My own belief is that physical activity is a real factor, but far more research is needed to show how great, if any, may be its effect.

Several items of information suggest that physical activity is not, by itself, a dominant factor. First, Kimura (1955) at Kyushu Medical School in Japan, where 100 per cent autopsy is the rule, found no significant difference between manual workers and mental workers in the incidence of severe atherosclerosis. Second, neither in Naples nor in southern Sweden were there significant differences between the serum cholesterol levels in men of equal age habitually engaged in different levels of physical activity, though there were major differences between the two countries at the same level of physical activity (Malmros and Biörck, 1954). Third, it is difficult to suggest that Englishmen and Swedes are very much less active than Italians or Spaniards and therefore the differences in the prevalence of coronary disease may be explained. Finally, in Japan, where coronary heart disease is so rare, there are hordes of men who do very little physical work. Clerks, petty officials, sedentary tradesmen, and relatively sedentary artisans form a very large group in Japan.

Emotion—"Stress and Strain"

Hours could easily be spent arguing about the question as to the role, if any, of emotion and the "stress and strain" of modern life on the production of coronary heart disease. One is tempted to quote the familiar verse:

> "Myself, when young did eagerly frequent,
> Doctor and Saint and heard great argument
> About it an about, but evermore came out
> By the same door as in I went."

But opinions are strongly held and stated in spite of the complete absence of objective evidence. Melville Arnott (1954) has well stated the case, from what is known at present, against blaming stress and strain. This should not deter us from urging that this shadowy area be subjected to systematic critical inquiry. Until then, however, there is really almost nothing to say beyond noting that life in Japan scarcely seems free from stress and strain and that even the Bantu has emotional problems.

TABLE VI.

The socio-economic factor in the distribution of kinds of heart disease as illustrated by data for Amritsar, India, on the percentages of coronary heart disease patients and of patients with rheumatic heart disease contributed by the three major social classes. Data from Malhotra (1951).

Class	Coronary	Rheumatic
I	31%	7%
II	54%	49%
III	15%	44%
All	100%	100%

Diet

So far this discussion has led mainly to negative conclusions. No major, primary role in atherogenesis or in the production of clinical coronary heart disease can be assigned to race, nationality, obesity and overweight, cigarette smoking or indulgence in alcohol. Some of these factors may make a secondary contribution, perhaps contingent upon the existence of a particular set of circumstances.

The relegation of physical activity to a minor place is made with more reservation but we still have little that is positive to go on. Finally, even sex may have its limitations.

But when we come to the diet, apart from sheer calories, there is much firmer ground to conclude that it is of major, primary importance. The evidence is consistent in theory, in field studies, in statistics, and in experiments, both on man and animals. But the evidence on the diet, is now so extensive that I refrain from attempting to summarize it here. I have written a good deal on the subject (Keys, et al, op. cit.; Keys, op. cit.).

During the past several years I have attempted to test the theory of a dominant effect of the dietary fat in studies on various natural populations as well as in controlled laboratory experiments. And so far all of the new evidence conforms to the concept presented in lectures in 1952 in New York, in Edinburgh, and in Amsterdam.

TABLE VII.

Serum total cholesterol concentration, mg. per 100 ml., in clinically healthy men habitually engaged in moderate physical activity. For 118 men of Cagliari, Sardinia, the values under "A" were obtained by analysis of the fresh serum in Italy while those under "B" were from aliquots sent to Minneapolis and analyzed there. The values for 150 Swedes of Malmö were obtained by Doctors H. Malmros, G. Biörck and B. Swahn by the same method as used in Italy.

Age	Cagliari		Malmö
	A	B	
19-29	160.7	160.6	189.5
30-39	170.2	168.5	210.3
40-49	193.8	194.7	237.2
50-59	190.4	190.4	236.0

Later in this symposium, Dr. Brock will present some of the new data from South Africa. Here I shall mention briefly only a few other points.

First, exact comparability of serum cholesterol values in the different field studies has now been checked. An example is given in Table VII. We have been able to make duplicate analyses at the place of blood sampling in the field and, again, at the laboratory here in Minneapolis. Measured aliquots of serum are dried on filter paper and sent by letter mail. The example summarized here is from Sardinia. Similar good agreement was obtained in the same way with bloods drawn in other parts of Italy as well as in South Africa.

Second, the data from Sardinia illustrate again the rule that when two populations are compared, the average serum cholesterol concentrations at given age correspond with the percentages of calories provided by fats in the habitual diets of those populations. Table VII compares these men of Cagliari, Sardinia, with men of Malmö, in southern Sweden, who were studied last year by Malmros, Biörck and Swahn after our joint work in Naples. All of these men were engaged in moderate physical activity in their jobs, the Swedes being firemen, the Sardinians being mainly firemen and policemen on outside duty. The general dietary level of the Swedes provides about 38 per cent of calories as fats, while the figure for the Sardinians is about 22 per cent. Both Professor Malmros and Dr. Paul White are here and may wish to comment on the obvious fact that coronary heart disease in southern Sweden is a great deal more prevalent than in Sardinia. The Sardinians are similar to the Neapolitans in this respect.

Third, there is no time here to discuss the interesting question as to the relative cholesterogenic action of different dietary fats. After five years of controlled dietary experiments on human subjects here in Minnesota we can say positively that all fats are *not* equivalent in this respect but that the differences in their effects are not explicable on a simple basis such as relative saturation or iodine number. For example, it may be noted that in controlled experiments on man there is little difference between cottonseed oil and olive oil in their effects on the blood cholesterol. These two fats are interesting, of course, because they differ greatly in the degree of saturation of the fatty acids.

In this connection, it is relevant to cite recent results of Donath et al (1954) who have carefully studied the diets and serum cholesterol of *true* vegetarians in Leiden, the Netherlands. As compared with ordinary Dutchmen (skilled laborers) in the same area, neither the average serum cholesterol nor the proportion of fat calories in the diet differed significantly. But, of course, the vegetarians got only vegetable fats while most of the fat in the diets of the non-vegetarians was provided from animal sources.

Summary and Conclusions

This discussion has reviewed, all too hastily, evidence and reasoning that must be considered in any attempt to explain why there are such great differences between men, and women too, in the tendency to develop severe atherosclerosis and die of coronary heart disease. No convincing brief can be filed for primary importance of heredity, overweight *per se*, the body form, the use of tobacco or alcohol. And it is obvious that being a male is not necessarily fatal.

Physical activity, too, as a factor may be questionable if we demand to be shown that the relatively favorable mortality of manual workers in some populations is unrelated to dietary and other factors. Future research should be planned to test more rigorously the hypothesis that the habitual physical activity has an important influence.

I believe that a powerful effect of the diet on human atherogenesis can no longer be doubted. Though it is easy to point to many unanswered questions about the effect of the diet, it is more and more clear that there is a broad interrelationship between the dietary fats,

(Continued on Page 783)

Lipoprotein Metabolism in the Etiology of Atherosclerosis

CHRISTIAN B. ANFINSEN, JR.
Bethesda, Maryland

THE occurrence of abnormalities in lipoprotein metabolism may bear a direct causal relationship to atherogenesis. At the present time, however, such a relationship is almost entirely inferential and it is the purpose of this summary to consider, as objectively as possible, the experimental findings and personal convictions which have led to this point of view.

It is now abundantly evident that lipids exist in animal tissues and fluids in the form of lipoprotein complexes and that the metabolic reactions which these substances undergo in an aqueous environment are made possible by the existence of such macromolecules. The direct or indirect involvement of lipids and, in particular, of cholesterol, in atherogenesis is strongly indicated by the chemical and pathologic data that have accumulated from investigations on vessel wall tissue exhibiting atheromatous degeneration. The study of metabolic derangements resulting in such lipid deposition were given fresh impetus by the introduction by Pedersen,[1] Gofman et al[2] Russ, Eder and Barr[3] and others, of the concept of a cause and effect correlation between the levels of certain circulating lipoproteins and the incidence of atherosclerotic heart disease. The elegant methodology introduced by Gofman and his collaborators for the analysis of plasma for its various lipoprotein components must be given particular mention in connection with the stimulation of new approaches to the study of the biochemical and physiological background of this disease. Studies with these physical techniques, as well as by other less complicated but equally useful chemical methods[4,5,6] have also shown a relative elevation of low-density lipoproteins in the plasma of males in relation to females, in the aged in relation to the young, and in connection with those diseases which appear to involve abnormalities in lipid metabolism and predispose to atherosclerosis, such as diabetes and nephrosis. An extensive consideration of these physiological studies and of the chemical literature pertinent to them cannot be attempted in the present discussion. Such summaries have appeared in a number of review articles.[7,8,9,10,11] We shall deal here, instead, with the enzymatic and physicochemical aspects of lipid absorption and transport in an attempt to evaluate the present state of knowledge of these processes in terms of the physiologic and pathologic situations to which they appear to be related.

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

Chemical Nature and Enzymatic Degradation of Lipoprotein

In a consideration of lipoprotein metabolism we must necessarily confine ourselves to the lipoproteins of plasma and lymph since, although obviously of fundamental importance, the lipoproteins of tissue cells have not been adequately studied. As has been determined in a large number of laboratories, lipids are transported through the extracellular fluids in the form of three major macromolecular classes. The first class is comprised of the extremely large particles, generically known as chylomicrons, which appear post-absorptively in the normal lymphatic drainage of the intestinal wall. Although the basic chemical composition of these triglyceride-rich substances is relatively well known, their detailed architecture is at present a complete mystery and, as will become evident in the subsequent discussion, stands as a major missing item of information necessary for a rational description of lipid transport and mobilization.

The second class, termed beta lipoproteins, are molecules of uncertain heterogeneity containing protein to the extent of about 25 per cent of the particle weight and including varying quantities of cholesterol, phospholipid and triglyceride under different physiologic circumstances. The low-density lipoproteins found in elevated con-

TABLE I. EFFECT OF PREINCUBATION OF LIPOPROTEIN LIPASE WITH PYROPHOSPHATE

Experiment No.	Sodium Pyrophosphate	Heparin	Glycerol Production
	..moles	..	..mole
1			0.49
2		5	0.57
3	0.5		0.50
4	0.5	5	0.58
5	5.0		0.19
6	5.0	5	0.50
7	0.5*		0.27
8	0.5*	5	0.43

All the vessels contained 0.1 ml. of lipoprotein lipase.

* In these two experiments, 0.5 micromole of pyrophosphate was preincubated with 0.1 ml. of lipoprotein lipase for 30 minutes at room temperature. In the absence of pyrophosphate, there was no decrease in enzymatic activity during a preincubation periol at room temperature.

centrations in certain metabolic disorders are generally of this class, but contain unusually high levels of triglycerides.

The third class, the alpha lipoproteins, contain relatively more protein, and relatively less lipid than the beta lipoproteins and are, consequently, characterized by a higher density. Although the chemical composition of the protein moieties of the alpha and beta lipoproteins is reportedly quite similar, end-group analysis[12] and immuno chemical[13,14] study indicate a major structural and functional difference between these two classes of substances.

Both the relative[6,9] and absolute levels of the alpha and beta lipoproteins of plasma may be closely related to the occurrence of vascular degenerative changes. It is likely, however, that a fundamental understanding of atherosclerosis must finally rest on the elucidation of the mechanisms controlling the synthesis, degradation and resulting extracellular fluid levels of these materials. It is the conviction of most of the workers in this field that the transport and mobilization of lipids in the normal and abnormal animal subject may furnish the most easily approached reflection of these unknown controlling mechanisms.

Our own efforts during the past three years have been concerned to a large extent with the characterization of an enzyme system originally termed "clearing factor" but more accurately, in the light of recent findings, lipoprotein lipase.[15a,b] Our interest in this system developed from the original observations by Hahn[16] and from subsequent studies by Weld,[17] Anderson and Fawcett,[18] Graham et al,[19] and others. The basic observation that alimentary lipemia as well as lipemias present in certain diseases involving disorders in lipid metabolism could be "cleared" by the administration of heparin to the animal or patient led, initially, to the concept of a heparin-induced or activated plasma enzyme which attacked the triglycerides of chylomicrons and low-density beta lipoproteins. Various tissue factors and plasma proteins were postulated as essential components of this system in the early study of the clearing phenomenon.[20] However, only after the application of classical enzyme techniques has the true nature of this system been more closely delineated. Recent work by Edward Korn[15,21,22] in our laboratory suggests very strongly that clearing factor is a tissue enzyme rather than a plasma enzyme. Thus, extracts of acetone powder preparations of heart muscle and, particularly, of adipose tissue[23] yield clearing factor preparations of very high specific enzyme activity which can be shown to depend upon the presence of heparin for normal lipolytic action against the triglycerides of chylomicrons, low-density beta lipoproteins, and synthetic "chylomicrons" prepared by incubation of oil emulsions with certain plasma protein fractions. The heparin dependent enzyme is characterized by its specific ability to attack the triglycerides of lipoproteins and chylomicrons in contradistinction to the ordinary non-heparin dependent lipases present in intestinal secretions and, ubiquitously, in tissues whose specificities are directed toward the hydrolysis of non-protein bound triglyceride compounds. This marked specificity is the basis for the term "lipoprotein lipase."

In view of the fact that lipoprotein lipase is predominantly localized in tissues it now appears that, except for the low levels of this enzyme which have been demonstrated in some instances in normal plasma, the high levels of activity in post-heparin plasma samples probably indicate a spilling over of activated lipoprotein lipase from tissue sites into extracellular fluids. The activity of lipoprotein lipase prepared either from post-heparin plasma[25] or from tissue extracts[21] is strongly inhibited by protamine and elevated concentrations of inorganic salts as well as by a number of phosphate derivatives including pyrophosphate and various nucleotides. The question of the presence or absence of heparin as a component prosthetic group of the enzyme will only be unequivocally resolved

TABLE II. ABILITY OF DIFFERENT SERUM FRACTIONS TO ACTIVATE COCONUT OIL.

Experiment No.	Fraction	Serum Equivalent	Glycerol Produeed
		ml.	. .mole
1	None	0	0.06
2	Whole serum	0.2	0.86
3	. .1-lipoproteins	0.2	0.54
4	. .1-lipoproteins	0.4	0.86
5	. .-lipoproteins	0.2	0.14
6	. .-lipoproteins	0.4	0.14
7	Residual serum after removal of lipoproteins	0.1	0.06

The coconut oil was preincubated for 30 minutes at 37° with the fractions indicated before incubation with lipoprotein lipase. The substrate, enzyme, and other components were mixed at 0° and then incubated at 37°. All the vessels contained 0.2 ml. of 10 per cent albumin (pH 8.5), 0.02 ml. of 1 M CaCl2, 10 micromole of heparin, and 0.28 ml. of 0.25 M NH4Cl-NH3 buffer (pH 8.5) in a total volume of 1 ml.

when the enzyme has been purified to a state permitting direct analysis for this material. The evidence at present available permits only the conclusion that heparin is required for lipoprotein lipase *action* since the pyrophosphate inhibited enzyme may be reactivated by the addition of small amounts of heparin[21] (Table I).

The over-all reaction carried out by lipoprotein lipase can be summarized in the following equations:

A. Substrate

1. Chylomicrons, low-density β-lipoproteins
2. Synthetic "chylomicrons."
   Triglyceride emulsion + α-lipoprotein → "activated" triglyceride

B. Hydrolysis

"Activated" triglyceride
Lipoprotein lipase
$\xrightarrow[\text{or } Ca^{++}]{\text{albumin}}$
Complexed fatty acids + glycerol (+ mono & di-glycerides during early stages)

Experiments on the "activation" of synthetic oil emulsions by various plasma protein fractions prior to lipoprotein lipase action have indicated, as shown in the equations above, that the most potent activating component in plasma is the alpha lipoprotein moiety. One such experiment on the triglyceride-activating effect of various plasma components is shown in Table II.[22] It can be seen from the data in this table that the alpha lipoprotein component accounts for essentially all the activating effect of serum since both the beta lipoprotein fraction and the residual serum proteins present after removal of the lipoproteins by ultracentrifugal flotation are almost completely without effect. These findings on the activation of triglyceride emulsions for lipoprotein lipase action suggest that the system described in the equations above may, indeed, be a model for a cyclic mechanism for the transport of neutral fat from the intestine to metabolically active tissues (Fig. 1).

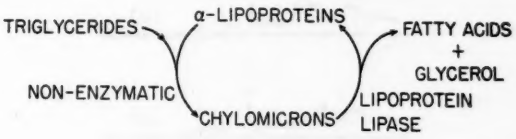


Fig. 1.

As can be seen from the equations above, the hydrolysis of lipoprotein-triglyceride requires the presence of certain fatty acid acceptors and binders which may be either divalent cations or serum albumin. Although possible fatty acid binders during the intracellular action of lipoprotein lipase may be divalent cation, or specific cellular proteins, the major transport form in the circulating blood of the unesterified fatty acids resulting from lipoprotein lipase and other possible lipolytic action is almost certainly the serum albumin-fatty acid complex.[26,27]

In earlier experiments on the electrophoretic mobility of plasma proteins following the administration of heparin to hyperlipemic patients it was found that the mobility of a portion of the beta globulin peak was markedly shifted as a result of complex formation with fatty acids liberated during the clearing reaction. Thus, in Figure 2 it can be seen that a portion of the beta globulin peak has shifted to a position in the electrophoretic pattern into and beyond the area occupied by serum albumin (Fig. 2, b, c, d). With time the mobility of this protein component returns to its initial value as in Figure 2f. Such electrophoretic changes could be induced equally well by the addition of an amount of sodium oleate approximately equivalent to that released under the conditions of the *in vivo* clearing. In later experiments, however, it has been shown that serum albumin, possessing a higher affiinity for fatty acid is the major vehicle for fatty acid transport. As has been demonstrated a number of times previously, the electrophoretic mobility of serum albumin varies in proportion to the unesterified fatty acid level with which it is in equilibrium up to the maximum level of its effective binding capacity. In general, it would appear that, except

for the situation in which large doses of heparin are administered to hyperlipemics, unesterified fatty acid transport in plasma is normally carried out entirely by serum albumin.

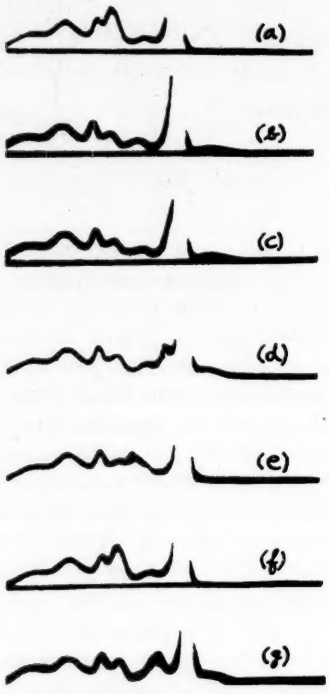


Fig. 2.

Physiological and Clinical Evidence Supporting the Importance of Lipoprotein Lipase in Normal Fat Metabolism

The importance of the lipoprotein lipase system in the regulation of fat transport and metabolism is suggested by several physiological observations in both animals and humans. In the light of *in vitro* chemical studies on the inhibitory effect of protamine[20] on lipoprotein lipase, Bragdon and Havel have carried out experiments[28] on the nature of the plasma lipoprotein picture following protamine administration in fasting rats. Their results are summarized in Figure 3. It can be seen that the administration of protamine resulted in a rapid and quantitatively significant increase in total plasma lipids which decreased to normal levels with time. They found, in addition, that this transient increase in plasma lipids could be accounted for by a specific rise in the triglyceride-rich beta lipoproteins of low density. The effect of protamine was reversed by the administration of heparin.

A clinical observation has recently been made by Havel and Gordon[29] which may represent an

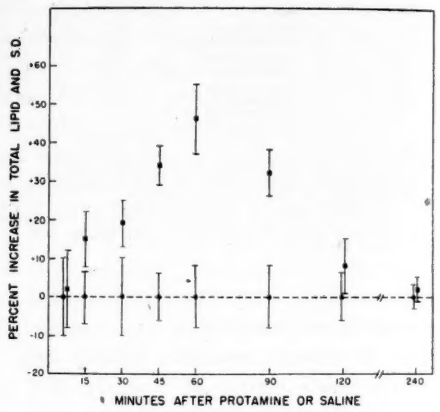


Fig. 3.

abnormal metabolic situation which is mimicked by the protamine experiments above. In a patient with idiopathic hyperlipemia and in two hyperlipemic siblings it was shown that the administration of anticoagulant doses of intravenous heparin did not lead to the production of more than minute traces of plasma lipoprotein lipase although the abundant appearance of this enzyme has invariably been observed in other individuals given such treatment. The excess lipid in this patient's plasma was present entirely in particles having the flotation and chemical characteristics of chylomicra. Alpha and beta lipoprotein concentrations were markedly reduced. On a fat-free diet his serum triglyceride content fell to within normal limits and the alpha + beta lipoprotein concentrations increased. Caloric restriction and repletion while the patient was on the fat-free diet failed to produce significant alterations in serum lipid and protein concentrations although the R.Q. during restriction was reduced to 0.73. This suggests that endogenous lipid transport was being effected but perhaps by a mechanism differing from that of exogenous lipid transport. Acute and intensive heparin administration failed to reduce significantly the patient's abnormal lipoprotein and triglyceride concentrations. Although an assumption must be made in suggesting that the observed defect in lipoprotein lipase

activity may account for the slow rate of removal of ingested fat from the blood in this patient, such an assumption does receive a certain degree of support from our present knowledge concerning the properties and distribution of lipoprotein lipase.

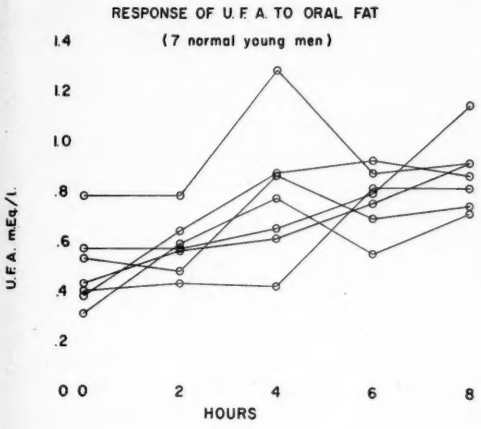


Fig. 4.

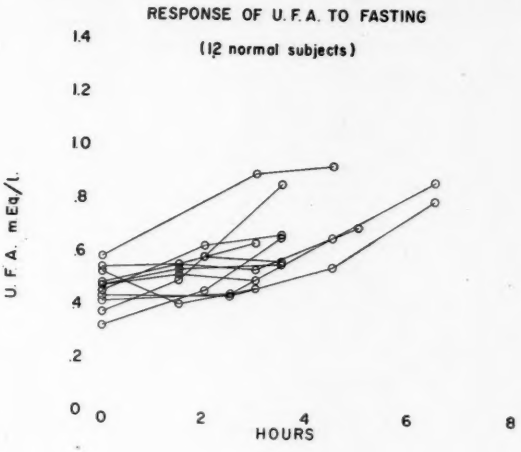


Fig. 5.

Finally, let us consider a series of observations[30a,b] recently made by R. Gordon and Amelia Cherkes in connection with the regulation of the unesterified fatty acid levels of circulating blood. The unesterified fatty acids (UFA) of normal blood, both in males and females, is approximately 0.5 milliequivalent per liter. Following the administration of oral fat to individuals fasted overnight, there is a moderate increase in this level, which persists for many hours (Fig. 4). Further experiments, however, showed a similar increase in blood unesterified fatty acids following fasting (Fig. 5), and suggested that the increased blood fatty acid level observed following oral fat was not due to the fat itself, but to the homeostatic influences leading to the degradation of depot fat in response to reduced blood glucose levels. The administration of oral glucose (Fig. 6) led to a marked decrease in the blood unesterified fatty acid level, followed by a marked rise after approximately two hours. In view of the well-known delayed hypoglycemia observed following glucose administration, which is believed to involve a homeostatic release of epinephrine, experiments were carried out on the effect of infused epinephrine on the plasma levels of unesterified fatty acids. It can be seen in Figure 7 that epinephrine has a marked effect, doubling or more than doubling the concentration of these substances in the individuals tested.

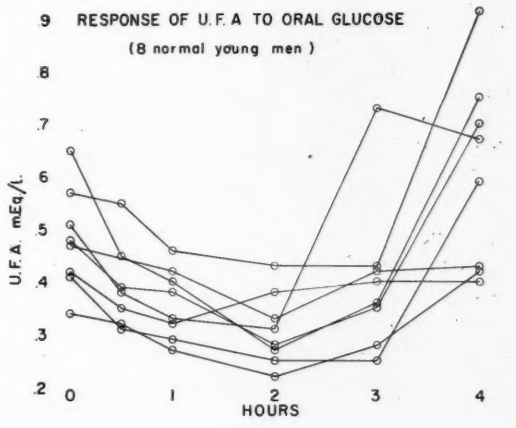


Fig. 6.

Studies with C^{14}-labelled long-chain fatty acids have been carried out in conjunction with these experiments by Havel and Fredrickson (unpublished results) as a means of labelling the triglycerides present in chyle. A study of the distribution of radioactivity in the various lipid fractions of blood following the infusion of such labelled chylomicrons suggests that the triglycerides of chyle are carried to tissues (mainly adipose?) and there deposited and, when required for nutritional purposes, re-secreted into the circulating blood as unesterified fatty acid. This over-all process may occur without direct metabolic involvement of the normal alpha or beta

components of plasma since the specific activity of the blood unesterified fatty acids was nearly as high as the specific activity of the fatty acids in the triglycerides of the infused chylomicrons

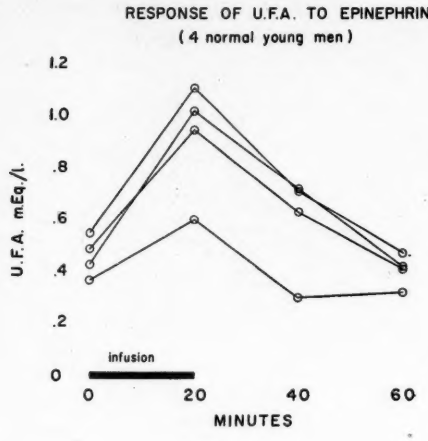


Fig. 7.

(free fatty acids were present in almost undetectable quantity in the administered chylomicrons) and since the radioactivity present in the plasma unesterified fatty acid fraction was found to increase earlier and more rapidly than that of the lipoprotein components of plasma.

Experiments on the arteriovenous differences in plasma fatty acid levels[30a] have emphasized their metabolic importance and short half-life. Indeed, it can be calculated, in the case of myocardium, that the fatty acids removed by this tissue can account in several instances for the major share (as much as 70 per cent) of its caloric requirements. In the case of arteriovenous difference studies on samples drawn from arterial blood and from the inferior or superior vena cava, a negative arteriovenous difference is observed, indicating the release of fatty acids from the adipose-rich areas supplied by this circulatory pathway.

General Consideration of Triglyceride Transport and Metabolic Homeostasis

It is of interest to attempt to trace the path of ingested lipid material from the chyle through the metabolic tissues of the body in relation to the enzymatic, physical and physiological observations outlined above. Evidence from a number of laboratories supports the view that triglycerides are probably extensively hydrolyzed in passing from the gut through the intestinal wall into the chyle possibly in combination with alpha lipoprotein (as in Figure 1) and surrounded with a serum albumin sheath. Such a conclusion is based on the finding that triglycerides, labelled by radioactive means or fed with a known synthetic arrangement of fatty acids in the triglyceride molecule,[31] are randomized in the chylomicron triglycerides with respect to the hydroxyl groups on the glycerol moiety to which they are esterified. The studies with radioactive isotopes described in the previous section suggest that this newly formed triglyceride passes as chylomicrons to metabolizing tissues and depot areas as shown in Figure 8 and that subsequently, depending on nutritional situations in the plasma and on resulting hormonal control (Regulatory Mechanism No. 1 in Figure 8) as suggested by the epinephrine studies, are either stored as triglyceride or secreted as unesterified fatty acid for transport to other areas of the body.

Direct measurements of the arteriovenous differences across the myocardium of unesterified fatty acids, glucose, and oxygen have added support to this scheme. Thus under conditions of lowered blood sugar levels, fatty acid utilization accounts for a large share of the caloric requirements of the myocardium. Upon intravenous administration of glucose, the energetic economy of the muscle shifts to carbohydrate, and the arterial and venous levels of unesterified fatty acids are essentially identical. Of particular interest is the finding that the UFA level *entering* the myocardium is markedly decreased following glucose administration, suggesting that the blood carbohydrate level has, through hormonal interactions, decreased the release of UFA from adipose areas.

The physiological observations described earlier, in which either protamine administration in animals (and perhaps in what may be construed as a genetic defect in the patients unable to produce lipoprotein lipase) suggest that in addition to the triglyceride-fatty acid transport system conditioned by glucose levels in the blood, there may also be a secondary mechanism in which lipid is transported (Regulatory Mechanism No. 2) when needed, in the form of lipoprotein-bound neutral fat. Such a mechanism would, then, become operative when the lipo-

protein lipase system was either absent, or unable to supply adequate supplies of foodstuff in the form of fatty acids. Such a mechanism would imply further the operation of phagocytic uptake of triglyceride-containing lipoproteins with subsequent metabolism through non-heparin-linked lipase systems. It is tempting to speculate whether or not the lipemia of starvation might not represent a situation in which elevated levels of plasma lipid are due, not to the absence of lipoprotein lipase as in the hyperlipemic siblings described above, but rather to a deficiency in hydrolyzable substrate in the extensively depleted depots.

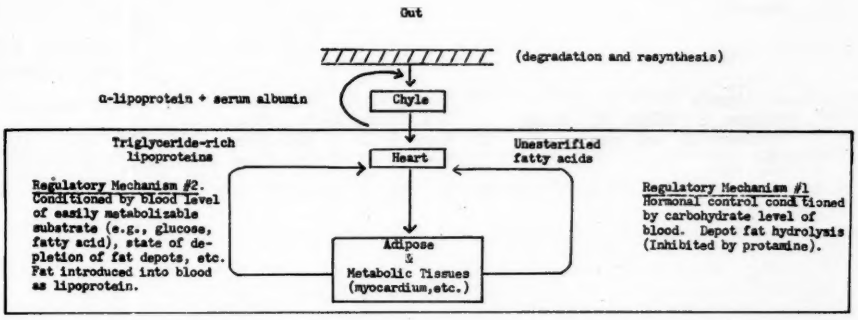

Out
(degradation and resynthesis)
α-lipoprotein + serum albumin
Chyle
Triglyceride-rich lipoproteins
Heart
Unesterified fatty acids
Regulatory Mechanism #2. Conditioned by blood level of easily metabolizable substrate (e.g., glucose, fatty acid), state of depletion of fat depots, etc. Fat introduced into blood as lipoprotein.
Adipose & Metabolic Tissues (myocardium, etc.)
Regulatory Mechanism #1 Hormonal control conditioned by carbohydrate level of blood. Depot fat hydrolysis (Inhibited by protamine).

Fig. 8. Scheme for triglyceride transport and metabolic homeostasis.

Direct support for Regulatory Mechanism No. 2 has come from further study of the protamine experiments described above (in which a transient lipemia was induced by administration of this material to fasting rats). Gordon and Bragdon have recently found that glucose, given simultaneously with protamine, completely prevents the lipemia observed in the protamine treated control rats with fasting blood sugar levels.

The discussion above cannot obviously be based in fact at the present time. Nevertheless the existence of the complex system of checks and balances known to be operative in carbohydrate metabolism must, it seems likely, find its analogy in the case of lipid metabolism. The specificities and properties of the lipoprotein lipase system may furnish a useful experimental wedge in the study of these phenomena, particularly in the light of the admittedly meagre though stimulating physiological observations that have begun to accumulate.

Atherosclerosis and Lipoproteins

It is clear that little more can be said, specifically, to relate lipoprotein metabolism to the process of atherogenesis. The suggestion has been made[82] that the slow but significant filtration of plasma proteins through tissues into the lymph might, in part, account for the early stages of vascular degeneration. Thus large lipid-laden lipoproteins are incompletely removed from the wall of the vessel or from the intervascular tissue areas through which they have filtered and may remain, after variable degrees of degradation, as centers for subsequent fibrosis and degeneration. Such a mechanism might well be augmented by local tissue damage or by hydrostatic effects peculiar to the area in question.

A great deal has been said in the past about the possible role of chemically and metabolically specific low-density beta lipoproteins as etiologic agents in atherosclerosis. The now well-established physical heterogeneity of the low-density beta lipoprotein spectrum of proteins considered in conjunction with the apparent immunochemical identity of these substances, make it begin to appear that the family of low-density beta lipoproteins may differ from one another only in the degree to which they are laden with non-specifically bound triglyceride, phospholipid and cholesterol. Should it evolve, through further study, that low-density lipoproteins are, indeed, a direct causal agent in atherogenesis, it seems not unlikely that their deleterious effects might be due in large part to their molecular size and to the metabolic problem they present to the tissues into which they penetrate. Even the much

maligned cholesterol molecule may ultimately become secondary in importance to the problem of neutral fat transport and metabolism.

The author is extremely grateful to his colleagues, Drs. Bragdon, Gordon, Havel, Korn, Fredrickson and Steinberg for their generous help and advice in the assembly of this discussion.

References

1. Pedersen, K. O.: Ultracentrifugal studies on serum and serum fractions (Uppsala, 1945).
2. Gofman, J. W.; Lindgren, F.; Elliott, H.; Mantz, W.; Hewitt, J.; Strisower, B., and Herring, V.: Science, 111:166, 1950.
3. Russ, E. M.; Eder, H. A., and Barr, D. P.: Am. J. Med., 11:468, 1951.
4. Hillyard, L. A.; Entenman, C.; Feinberg, H., and Chaikoff, I. L.: J. Biol. Chem., 214:79, 1955.
5. Havel, R.; Eder, H., and Bragden, J.: J. Clin. Invest. (in press).
6. Eder, H. A.: Symposium on Atherosclerosis. National Academy of Sciences, National Research Council, 1955.
7. Jones, H. B.; Gofman, J. W.; Lindgren, F. T.; Lyon, T. P.; Graham, D. M.; Strisower, B., and Nichols, A. V.: Am. J. Med., 11:358, 1951.
8. Gould, R. G.: Am. J. of Med., 11:209, 1951.
9. Anfinsen, C. B.: Symposium on Atherosclerosis. National Academy of Sciences, National Research Council, 1955.
10. Anfinsen, C. B.: In: Fat Metabolism, edited by V. A. Najjar. Baltimore: Johns Hopkins Press, 1954.
11. Nikkilä, E.: Scand. J. Clin. and Lab. Invest., 5: supplement 8, 1953.
12. Avigan, J.; Steinberg, D., and Redfield, R.: Unpublished results.
13. Brown, R. K.: Personal communication.
14. Avigan, J.: Unpublished results.
15. (a) Anfinsen, C. B.; Boyle, E., and Brown, R. K.: Science, 115:583, 1952.
    (b) Korn, E. D.: Science, 120:399, 1954.
16. Hahn, P. F.: Science, 98:19, 1943.
17. Weld, C. B.: Canad. M. A. J., 51:578, 1944; Proc. Canad. Physiol. Soc., 1948.
18. Anderson, H. G., and Fawcett, B.: Proc. Soc. Exper. Biol. & Med., 74:768, 1950.
19. Graham, D. M.; Lyon, T. P.; Gofman, J. W.; Jones, H. B.; Yankley, A.; Simonton, J., and White, J.: Circulation, 4:666, 1951.
20. Brown, R. K.; Boyle, E., and Anfinsen, C. B.: J. Biol. Chem., 204:423, 1953.
21. Korn, E. D.: J. Biol. Chem., 215:1, 1955.
22. Korn, E. D.: J. Biol. Chem, 215:15, 1955
23. Korn, E. D., and Quigley, T. W., Jr.: Biochim. et Biophys. Acta (in press).
24. Jeffries, G. H.: Quart. J. Exper. Physiol., 39:77, 1954.
25. Anfinsen, C. B., and Quigley, T. W., Jr.: Circulation, 8:435, 1953.
26. Gordon, R. S.; Boyle, E.; Brown, R.; Cherkes, A., and Anfinsen, C. B.: Proc. Soc. Exper. Biol. & Med., 84:168, 1953.
27. Gordon, R. S., Jr.: J. Clin. Invest., 34:477, 1955.
28. Bragdon, J., and Havel, R.: Am. J. Physiol., 177: 128, 1954.
29. Havel, R., and Gordon, R. S., Jr.: Abstract, American Society for the Study of Arteriosclerosis, 1955.
30. (a) Gordon, R. S., Jr., and Cherkes, A.: In press.
    (b) Dole, V.: In press (personal communication).
31. Bergstrom, S.; Borgstrom, B., and Carlsten, A.: Acta Physiol. Scand., 32:94, 1954.
32. Kellner, A.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council, 1955.

COLDS AND RESPIRATORY INFECTIONS IN THE CARDIAC PATIENT

The question, "How important are respiratory infections as a cause of heart failure?", is examined in a recent issue of *Diuretic Review.*

Recently published papers in the professional literature point to general agreement, *Diuretic Review* reports, that respiratory infections, particularly colds, are the most common irritating and aggravating factors in congestive heart failure.

In a study of more than 300 cases of heart failure, a British medical investigator found more than half with some type of respiratory infection.

Furthermore, it was established that the infection was the precipitating cause of decompensation in 156 of the 300 cases. In a similar study conducted by three investigators and reported in the *American Journal of Medical Science,* a direct relation was found between the frequent occurrence of heart failure among cardiac patients and onset of "even minor colds."

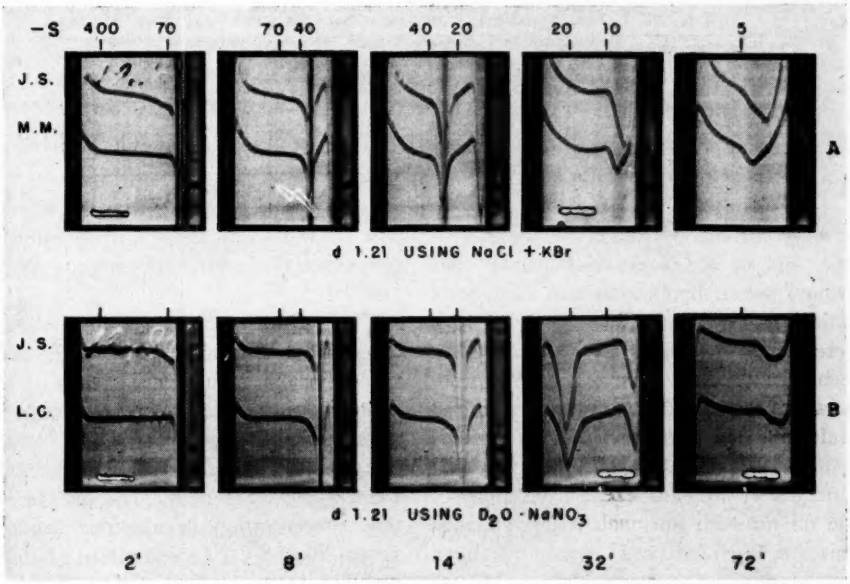
The British investigator, Dr. F. J. Flint, believes respiratory infection in the person with a weak heart may initiate cardiac failure by causing damage to the heart muscle or by favoring congestion of the lungs.

Under any circumstances, *Diuretic Review* points out, these studies emphasize the importance of looking for and treating respiratory infection in cardiac patients.

The Lipoprotein System

LENA A. LEWIS
Cleveland, Ohio

MANY methods of investigation of lipoproteins have been developed since the original description of a lipoprotein in 1929 by Macheboeuf.[1] The application of high density ultracentrifugation for the concentration of serum lipoproteins by Pedersen,[2] and of the using NaCl and KBr.[4] If the preparative ultracentrifugation is carried out for seventeen hours at 16° to 18° C., a lipoprotein concentrate is obtained, which in the case of KBr·NaCl system contains most of the serum lipoprotein. Figure 1 (a) shows the type of pattern obtained



Comparative flotation rate of human serum lipoproteins studied at a density of 1.21 using, (a) NaCl + KBr, and (b) $D_2O \cdot NaNO_3$, in the analytical ultracentrifuge at 52,640 r.p.m.

analytical ultracentrifuge for their characterization by Gofman and co-workers,[3] provided a great impetus to further studies as to their nature and physiology.

The studies of serum lipoproteins to be reported here were carried out by ultracentrifugation either at a density of 1.063 using NaCl, as originally described by Gofman,[2] or at d 1.21 on normal serum using d 1.21, KBr·NaCl. A few studies were also made at density of 1.21 using D_2O and $NaNO_3$.[5] When this system is employed, longer preparative centrifugation at a higher "g" is necessary to obtain satisfactory lipoprotein concentration. Comparison of flotation rates at d 1.21 with the two systems (Fig. 1, a and b) shows a considerably slower rate with the D_2O-$NaNO_3$ system. If centrifugation is carried out for a sufficiently long time, a like degree of resolution is obtained.

The question, "What is the serum lipoprotein pattern of the normal adult human being?", is frequently asked. A group of normal controls

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio.
This was supported by a grant from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland.
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

TABLE IA. SERUM PROTEINS, ELECTROPHORETIC TECHNIQUE, OF CLEVELAND CONTROLS, PERUVIAN AND NAVAJO INDIANS AND CLOISTERED MONKS.

	Total Protein	A+α_1-globulin		α_2-globulin		β-globulin		γ-globulin		
	gm.	gm.	%	gm.	%	gm.	%	gm.	%	Age
Cleveland Controls Mean	7.44±	4.74	63.5±	0.54±	7.2±	1.11±	15.2±	1.04±	14.1±	29.5±
S. E. of Mean	0.15	±0.11	1.09	0.04	0.36	0.03	0.40	0.05	0.56	1.72
Peruvian Indians Mean	7.53±	4.34±	57.8±	0.52±	6.93±	1.17±	15.6±	1.49±	19.0	27.5±
S. E. of Mean	0.17	0.12	2.2	0.04	0.40	0.09	0.65	0.11	±1.57	2.6
Navajo Indians Mean	6.69±	3.25±	48.6	0.66	9.9	1.21±	18.2±	1.56±	23.2±	56.0±
S. E. of Mean	0.23	0.08	±1.0	±0.04	±0.52	0.03	0.54	0.08	1.08	3.2
Monks Mean	6.92±	4.44±	64.1±	0.39±	5.8±	1.08±	15.1±	1.00±	15.4±	30.3±
S. E. of Mean	0.11	0.10	1.40	0.05	0.70	0.05	0.72	0.06	0.75	3.4

TABLE IB. SERUM LIPOPROTEINS, ULTRACENTRIFUGAL TECHNIQUE D 1.21, USING KBR + NACL, OF CLEVELAND CONTROLS, PERUVIAN AND NAVAJO INDIANS AND CLOISTERED MONKS.

	Total Chol. mg./100ml.	-S70-400 mg./100ml.	40-70 mg./100ml.	25-40 mg./100ml.	20-25 mg./100ml.	1-10 mg./100ml.
Cleveland Controls Mean	229.7±	36.7±	24.2±	>220	11.6±	176.9±
S. E. of Mean	4.4	3.8	1.8		1.8	6.5
Peruvian Indians Mean	186.0±	91±	33±	208±	18.0±	197.5±
S. E. of Mean	11.8	14.1	3.6	16.7	4.2	17.6
Navajo Indians Mean	175±	17±	23±	206±	13.0±	172.9±
S. E. of Mean	6.2	2.6	2.4	9.1	1.5	9.7
Monks Mean	184±	34±	34.6±	197±	14.0±	124.2±
S. E. of Mean	14.9	4.5	4.6	18.7	2.0	20.7

was selected from the personnel of the Cleveland Clinic, and of a Cleveland industrial concern in whom serum lipoprotein and cholesterol determinations were made. Two-thirds of this group were male. A similar group had previously been analyzed as normals for serum electrophoretic proteins. We have also compared sera of fourteen normal male Peruvian Indians living at high altitudes with those of fifty-five Navajo Indians of mixed sexes. Serum analyses were done on nineteen normal cloistered monks on a uniform, well-balanced dietary regimen which contained about protein 51, fat 34 and carbohydrate 267 gm. per day, equivalent to 1,591 cal.

Diet of the Peruvian natives contains very little fat and the main caloric source is vegetables and a little meat. The Navajo Indian diet, unlike that of the Peruvian Indians, is not low in fat but similar to that common to Americans generally.

Table I, a and b, summarizes the lipoprotein and electrophoretic protein data obtained on the four groups. The serum total protein of the Cleveland controls and that of the Peruvian Indians were nearly the same, except that the concentration of albumin was lower and that of the γ-globulin higher in the Peruvians. These differences were even more intense in the Navajo. The total protein of the monks was lower than that of the Cleveland controls, but the relative proportions of the various proteins were very similar.

The means of total serum cholesterol in all three selected groups were lower than that of the Cleveland group. The means of $-S_{25-40}$ lipoproteins of the three special groups were consistently lower than that of the "controls." The $-S_{1-10}$, α_1-lipoprotein, was lower in the monks than in the other three groups. The α_2-lipoprotein concentration in all four groups was the same. The $-S_{40-70}$ concentration of the Peruvians and monks was very slightly higher than the Cleveland control and Navajo groups. The $-S_{70-400}$ fraction of the Peruvians was higher than the other groups. All blood samples were taken in the fasting state; this higher value is not attributable to an alimentary lipemia.

Atherosclerosis, for a number of reasons, is relatively uncommon in the American Indian. The data indicate an association of this trend in Navajos and Peruvians with a relatively low concentration of serum β-lipoprotein and with relative increases in γ-globulin.

Some of the differences between the groups may be due to their varied dietary habits; in the case of the Peruvian Indians who lived at an altitude of approximately 3,750 meters environment may have played a part and genetic factors may have their effect.

The importance of heredity as a factor in establishing the lipoprotein pattern is emphasized by results obtained on two strains of dwarf pigs, the so-called long-lean, and the short-fat as bred at the University of Minnesota. Table II shows representative serum cholesterol and lipoprotein values obtained on a pig of each strain. While both strains of pigs received the same diet which consisted of SMA formula*, corn and oats, the concentrations of cholesterol and lower density -$S_{15-25,\ 25-40,\ 40-70}$ and $_{70-400}$ components were greater in the short-fat animal than in the long-lean.

TABLE II. SERUM LIPOPROTEIN PATTERNS OF LONG-LEAN AND SHORT-FAT STRAINS OF DWARF PIGS.

	Age	Serum Lipoprotein mg. per 100 ml.						Cholesterol mg. per 100 ml.	
		-S>400	70-400	40-70	25-40	15-25	1-15		
Long-lean Strain #6	4 mo.	++	7	0	56	33	212	111	5 hr. after feeding
Short-fat Strain #1	4 mo.	+++	30	9	82	52	235	166	5 hr. after feeding
Long-lean Strain #6	12 mo.	0	21	21	56	71	246	145	16 hr. after feeding
Short-fat Strain #1	12 mo.	0	49	35	114	106	198	188	16 hr. after feeding

TABLE III. SERUM LIPOPROTEINS OF FAMILY WITH HEREDITARY HYPERLIPEMIA, DETERMINED BY ULTRACENTRIFUGATION AT D 1.21 (NACL + KBR).

mg./100 ml. serum

	-S70-400	40-70	25-40	20-25	1-10	Chol.	Age
Father	223	42	82	70	136	151	72
Mother	177	132	>235	30	136	292	—
Son No. 1	382	82	110	63	176	333	37
Son No. 2	>300	62	98	43	115	248	27
Son No. 3	189	51	53	46	65	208	<27
Son No. 4	28	54	188	30	136	—	<27

Similarly importance of hereditary factors is evident in humans exhibiting hereditary hyperlipemia. Table III summarizes the serum lipoprotein data on such a family. Three of the four off-spring showed abnormally high concentration of -S_{70-400} components, while all four showed values of -S_{40-70} and $_{20-25}$ higher than normal for their age.

The lipoprotein pattern of a given normal individual varies relatively little over a period of years. In a group of seventy-seven studied yearly for three to five years those with high $S_{f\ 12-20}$ and $_{20-100}$ and cholesterol concentrations initially usually showed similar high values on subsequent studies and those with low values remained so. Table IV gives the results on three representative subjects.

TABLE IV. SERUM LIPOPROTEINS OF NORMAL INDIVIDUALS DETERMINED ULTRACENTRIFUGALLY AT D 1.063, AT YEARLY INTERVALS.

Subject No.	Date	Age at Initial Study	mg./100 ml. serum		
			Sf12-20	Sf20-100	Chol.
A	5-51	43	77	77	335
	5-52		84	88	335
	5-53		69	78	330
	5-54		62	146	348
B	3-51	51	33	50	—
	3-52		29	42	—
	3-53		43	67	257
	3-54		30	34	245
	3-55		20	64	252
C	6-51	48	20	12	—
	6-52		21	46	186
	6-53		19	45	179
	5-54		6	72	205
	5-55		6	31	196

While the lipoprotein pattern remains relatively stable when the animal is in good health and on a normal diet, rapid changes can be produced by disease or modification in diet. Recent studies carried out in collaboration with George Wilgram, University of Toronto, of lipoproteins of rats during choline deficiency showed a decreased concentration of the low density -S_{70-400} and of the α_1-lipoproteins in male rats fed a high fat, choline-deficient diet. It is interesting that despite the decreased concentration of lipoproteins the animals developed cardiovascular disease, i.e., cardiac necrosis, coronary lipidosis and aortic sclerosis.

The serum lipoprotein pattern of rats is greatly modified by the production of the nephrotic syndrome following injection of nephrotoxic serum.[6] Increased concentration of all lipoprotein components, but chiefly in the lower density fractions, is observed. Less severe changes of similar type occur in rats within

*We are indebted to Dr. George E. Farrar, Wyeth, Inc., for generous supplies of SMA.

forty-eight hours following unilateral nephrectomy and ureter ligation. Little change in the lipoprotein pattern is observed in the rat following bilateral nephrectomy. Thus the changes in the lipoprotein pattern of rats with renal lesions depend on the nature of the renal damage.

In contrast with rats, in the rabbit relatively great increases in serum low density lipoproteins and cholesterol occur following bilateral nephrectomy. Similar changes and of similar magnitude have been observed in rabbits' sera following DCA, cortisone, or DCA and renin treatment. The lipoprotein shifts in the rabbit seem to be produced more easily and from more varied factors than in the rat.

Summary

In any consideration of lipoproteins, the method of study, type of experimental animal used, hereditary, dietary, climatic background and physiological status of the animals, must be carefully evaluated. These and many more factors undoubtedly are involved in the lipoprotein story.

Bibliography

1. Macheboeuf, M. A.: Bull. Soc. Chim., 45:662, 1929.
2. Pedersen, K. O.: Ultracentrifugal studies of serum and serum fractions. Uppsala, Almquist and Wiksells Boktrycheri, A. B., 1945.
3. Gofman, J. W.; Lindgren, F. T.; Elliott, H.; Mantz, W.; Strisower, B., and Herring, V.: Science, 111: 166, 1950.
4. Lewis, L. A.; Green, A. A., and Page, I. H.: Am. J. Physiol., 171:391, 1952.
5. de Lalla, O. F., and Gofman, J. W.: Methods Biochem. Analysis, 1:459, 1954.
6. Lewis, L. A., and Heymann, W.: Proc. Soc. Exper. Biol. & Med., 86:766, 1954.

Discussion

ANCEL KEYS, University of Minnesota: Dr. Lewis' data on Navajo Indians are particularly interesting in view of her statement that these people live on a diet similar to that of Americans in general. If it is actually the case that the Navajo get something like 40 per cent of his calories from fats in the diet, then it is remarkable that the lipoprotein and cholesterol concentrations in their blood serum resembles those in serum from the Peruvian Indians whose diet is, as I can testify from personal experience, far lower in fats. It would seem to be most desirable to get detailed data on the diets of these Navajo Indians. In particular, it would be important to have information on the contribution of different types of fats to their total calories. For example, it is hardly possible that the adult Navajo has as high a consumption of butterfat as is customary here in Minnesota.

In Dr. Lewis' data it is notable that the Navajo Indians she studied are much older than the other groups. This means, of course, that their serum cholesterol and lipoprotein values are not comparable because in almost all population groups there is a great change from the values common to men of thirty years of age to those in men fifty-six years old. But this age difference, actually, only emphasizes the discrepancy with other data in the literature, including our own on two population groups of Spaniards, six of Italians, three of Swedes, two of Sardinians, nine of South Africans and three of Minnesotans.

So we should like to know the details of the Navajo diet, the relative obesity of the men, their habitual level of physical activity, and other items that may influence the picture.

The Monks studied by Dr. Lewis are reported to get about 35 per cent of their calories from fats in the diet. This is, of course, considerably less than the U. S. average and is in conformity with the reported values for their serum cholesterol.

In this connection it is of interest to note that Dr. J. Groen of Amsterdam has recently completed a study on a large number of Catholic Monks in two different orders in the Netherlands. When the averages of these are plotted for decades of age, both groups show the familiar rise of serum cholesterol with age until fifty or sixty years and some decline thereafter. But the serum cholesterol values for the Benedictines are much higher than for the Trappists at given ages. Further, it is interesting that Dr. Groen found many more very old Trappists than Benedictines, suggesting that there may be a real difference in longevity between them. In any case it will be noted that the Benedictines live, in regard to diet, much as do other Dutchmen. The Trappists, however, live on a very spartan diet.

COFFEE, CAFFEINE AND CHEMISTRY

Recent laboratory analyses indicate wide variations in the amount of caffeine extracted from various types of "regular" and instant coffee, according to Drs. Robert G. Martinek and Walter Wolman. In assays conducted in the chemical laboratories of the American Medical Association, the investigators found that although various brands of regular ground bean coffee did not vary significantly in caffeine-content, "Almost twice the amount of caffeine per cup can be obtained from the regular ground bean coffee as from the regular instant coffee; . . . Caffeine content per cup prepared from the regular ground coffee bean is roughly three times that of the regular decaffeinated coffee and about four to eight times that of instant decaffeinated coffee."—MARTINEK, R. G., and WOLMAN, W.: Xanthines, Tannins, and Sodium in Coffee, Tea, and Cocoa, *Journal of the American Medical Association*, 158:1030 (July 23) 1955.

Cholesterol Metabolism

IVAN D. FRANTZ, JR.
Minneapolis, Minnesota

THE importance of cholesterol metabolism as a field of knowledge in its own right is scarcely open to question. That this subject bears any direct relationship to human arteriosclerosis, or that it is entitled to a place on the program of a symposium such as this, is much more debatable. The general topic of cholesterol metabolism has formed the subject of two recent reviews.[1,2] It is appropriate, therefore, for me to confine my remarks to the question of its relationship to arteriosclerosis, either real or supposed. These remarks will necessarily be speculative, because actual knowledge is lacking.

It is well known that cholesterol is a principal constituent of the atherosclerotic plaque. Although the possibility has recently been raised that this cholesterol is synthesized in the arterial wall itself,[3] most observers are agreed that it is derived from the blood. Evidence is at hand to indicate that injury to the vessel wall can predispose to the deposition of cholesterol.[4,5] Elevation of the blood cholesterol, produced by experimental means in a variety of animals,[6,7,8,9] can also cause the formation of plaques. Since the blood cholesterol of man is higher than that of most other animals, it is understandable that this characteristic should have been given credit for the much higher incidence of atherosclerosis in man. Studies of patients with outspoken manifestations of atherosclerosis indicate that such patients have, on the average, an abnormally high blood cholesterol.[10,11,12] The correlation is so poor, however, that other important factors must also be involved. More or less successful attempts have been made to implicate the cholesterol to phospholipid ratio,[13] the distribution of cholesterol between alpha and beta lipoproteins,[14] and the size and composition of the lipoprotein molecules as measured by their rate of flotation in the ultracentrifuge.[15] In the discussion to follow, I am going to assume that, other things being equal, atherosclerosis develops more rapidly if the blood cholesterol is in a condition which favors its separation from its stable colloidal state, either due simply to a high concentration, or to the nature of the lipoprotein aggregate in which it is combined.

When a disease is characterized by the excessive accumulation of a normal bodily constituent, investigations are usually undertaken to determine whether the cause is overproduction or underutilization. It is possible that the high blood cholesterol in man will eventually be traced to one of these mechanisms. Personally, I doubt that either will prove to be the primary cause. This doubt is based on the extreme lability of hepatic cholesterol synthesis, and its strong dependence on external stimuli. Several laboratories have confirmed the observation of Gould and Taylor[16,17] that cholesterol synthesis is depressed by cholesterol feeding.[18,19,20] If a rat weighing 150 grams is allowed to eat a single dose of 100 mg. of cholesterol along with its normal food, its cholesterol synthesis the following morning, as judged by the liver slice technique, is depressed ten-fold. In interpreting these results, one must be wary of the possibility that the apparent depression is due, at least in part, to decreased specific activity of the carbon-labeled precursors of cholesterol (c.f. Medes, Spirtes, and Weinhouse[21]). Recent experiments by Loud, however, in which incorporation of carbon from acetate and of hydrogen from water were followed simultaneously, provide additional evidence that the depression is genuine.[22] We have also studied two stimuli (biliary obstruction and intravenous injection of a surface-active agent) which appear to produce a sudden, large increase in the rate of cholesterol synthesis.[23,24] This lability may be regarded as an important factor in the homeostatic regulation of the cholesterol content of the body. An increase in the cholesterol content of the diet or a change in the rate of excretion or destruction of cholesterol might be expected

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

The original work referred to was supported in part by a grant (No. H-1875) from the National Heart Institute, United States Public Health Service, and in part by anonymous donors.

to be nullified in large measure by an immediate change in the rate of cholesterol synthesis. It seems likely to me, therefore, that we must probe beyond the rates of synthesis, destruction, absorption, and excretion for the primary cause of the elevated blood cholesterol in man.

I should now like to suggest a point of view which may help to account for a number of the facts mentioned above. The central idea in this viewpoint is that the living organism is to be regarded as a multiphasic system in which the thermodynamic activity or "escaping tendency" of cholesterol tends to be equal in each of the several compartments and phases. This system is undoubtedly not in a condition of equilibrium with regard to cholesterol, because of the continual removal and addition of cholesterol at various sites; yet such changes are followed by secondary changes in the other compartments which tend to restore the equality of the cholesterol activity throughout. These secondary changes may include transfer of cholesterol from one compartment to another, as well as alterations in the rate of cholesterol synthesis.

As specific examples of the operation of the above process, let us consider the regulation of the rate of cholesterol synthesis in the rat. In this animal it appears proper to regard the serum and liver cholesterol as freely exchangeable.[25] Isotopically labeled material passes between these two compartments very readily.[24] The concentrations on the two sides of the partition, however, are quite different. In our experience, the concentration in the serum is about 70 mg. per 100 ml., and in the liver about 250 mg. per 100 grams wet weight.[20,23,24] Evidently the state of combination of cholesterol in the liver is such as to reduce greatly its escaping tendency. If cholesterol is added to the diet, most of it is promptly deposited in the liver. The serum cholesterol rises only if the feeding is continued to the point that the animal's defenses are overwhelmed. Coincident with the rise in the concentration in the liver, the rate of synthesis in that organ, as measured by various isotopic techniques, decreases dramatically.

If one ligates the rat's common bile duct, the serum cholesterol rises to a very high level, with little or no change in concentration in the liver. Although definite proof is lacking, we have explained this finding on the basis that the accumulation of bile acids has a stabilizing effect on the serum cholesterol. The activity of the latter is thereby reduced, and cholesterol is rapidly poured out of the liver to make up the deficit. This hypothesis, together with the apparent large and sudden increase in total body cholesterol, led us to predict that the rate of synthesis in the liver would be elevated. We confirmed this prediction by *in vivo* and *in vitro* techniques, with the use of both carbon-labeled acetate and tritium-labeled water. Similar studies on the rate of synthesis following intravenous administration of the surface-active agent Triton WR-1339 led to similar results.[24] This agent, as shown by others,[26,27] produces a rise in serum cholesterol which in our hands proved even more striking than that caused by biliary obstruction. The rise is sometimes as much as ten-fold in a twenty-four hour period. It is not surprising that the rate of synthesis should also be elevated.

We have previously emphasized the reciprocal relationship which exists between the rate of cholesterol synthesis after cholesterol feeding and the concentration of cholesterol existing in the liver. It occurred to us that if the notion is correct that it is the activity rather than the concentration which is the important factor in regulating the rate of synthesis, then it might be possible to upset the reciprocal relationship by a judicious combination of cholesterol feeding and ligation of the common bile duct. Such proved to be the case. Following biliary obstruction in the cholesterol-fed rat, the cholesterol accumulated in the liver is rapidly poured into the blood. At early time intervals after the ligation, however, the rate of synthesis is elevated above that, even, of normal controls, while the concentration in the liver has not yet fallen to normal. This finding is to be expected if we assume that the activity of cholesterol in the liver as well as in the serum is decreased by the accumulation of bile acids. The detergent Triton WR-1339 in combination with cholesterol feeding produced a somewhat different effect. As in biliary obstruction, the cholesterol accumulated in the liver was rapidly dissipated; but we were never able to attain conditions which led to a rate of synthesis greater than normal while the liver concentration remained elevated. This result would be expected if the effect of the foreign detergent is exerted entirely extra-

cellularly, in contrast to that of the bile acids, which themselves originate within the liver cells.

The concept of the regulation of cholesterol metabolism presented above represents a thermodynamic approach, and includes nothing about the actual mechanism responsible for the control of cholesterol synthesis. Some tentative ideas about the latter may also be drawn from the data available. One thinks first of the possibility that the enzyme responsible for the final step in the synthesis may be inhibited competitively by the product. In Figure 1, a calculated curve based on this possibility is superimposed on our data for the rate of cholesterol synthesis in liver slices as a function of cholesterol concentration. The agreement can be made to appear fairly good because of the large number of constants which remain adjustable for lack of experimental data. This agreement is not to be taken as evidence in favor of control by product inhibition. It is merely indicative of the fact that that mechanism cannot be eliminated on the basis of information now at hand.

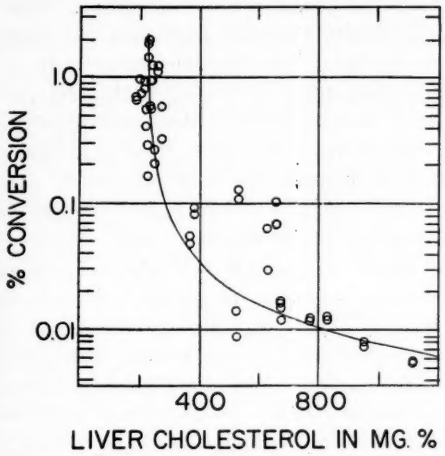


Fig. 1. Ability of liver slices to convert acetate to cholesterol, as a function of the concentration of cholesterol in the liver. The ordinate is the percentage of the radioactive acetate added which was converted to cholesterol in a 3-hour period. The curve was plotted from the equation for competitive inhibition,

$$V = \frac{V\frac{K_I}{K_m}S}{K_I + \frac{K_I}{K_m}S + I}$$

where v = velocity of the reaction, V = maximum velocity (enzyme saturated with substrate), S = substrate concentration, I = inhibitor concentration, K_m = equilibrium constant for the combination of substrate with enzyme, and K_I = equilibrium constant for the combination of inhibitor with enzyme. It was assumed that below a concentration of 222 mg./100 gm., all of the cholesterol is tightly bound and incapable of acting as an inhibitor. The following values were assigned to the components of the equation: V = 2.20 per cent, S = 1 mg./100 gm. (molecular weight of substrate assumed to be the same as that of cholesterol), K_m = 1 mg. per cent, K_I = 2.75 mg. per cent.

This figure (without the superimposed curve) was taken from reference 20, and I wish to thank the Journal of Biological Chemistry for permission to reproduce it.

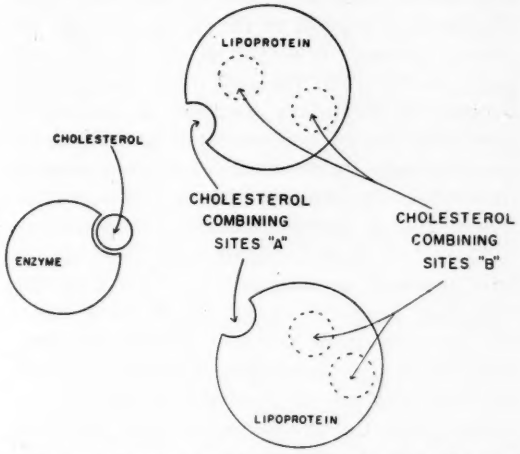


Fig. 2. Suggested scheme for the regulation of cholesterol synthesis. If sites "A," near the surface of the lipoprotein, are unoccupied, collisions of the lipoprotein with the enzyme will usually result in removal of the cholesterol from the enzyme and will permit the latter to begin the synthesis of a new molecule. Sites "B" are to be thought of as more numerous but less readily accessible. After sites "A" are filled, collisions become progressively less effective in removing cholesterol. If the "A" sites and most of the "B" sites as well are filled as a result of cholesterol feeding, collisions are rarely effective and synthesis drops to a very low level.

It seems improper to me to think of cholesterol synthesis in the terms used in the preceding paragraph, because of the extremely low water solubility of cholesterol unassociated with protein and phospholipid. A more promising viewpoint is to assume that a cholesterol molecule, once it is formed on the surface of the enzyme, must remain there until it is removed by collision with a lipoprotein molecule capable of accepting it. The enzyme would remain unable to initiate the synthesis of another molecule until such an encounter has taken place. Lipoproteins presumably contain a number of sites which can be filled by cholesterol. A few of these are probably near the surface, so that they can be filled very readily in the event of a collision with an enzyme carrying a cholesterol molecule. Most of the sites are probably in the interior or "core" of the lipoprotein aggregate, and the

likelihood of their being filled is small, even in the event of a collision. If the animal's store of cholesterol is small, most of the sites are empty, including those easily filled. Collisions with enzyme molecules carrying cholesterol usually result in removal of the cholesterol, and the rate of synthesis is very high. As the sites are progressively filled, the rate of synthesis falls. Presumably there is a spectrum of cholesterol sites, with respect to accessibility, and this spectrum accounts for the observed relation between cholesterol concentration and rate of synthesis. Figure 2 is an attempt to clarify this notion.

The effect of surface-active agents on cholesterol synthesis is also understandable from the viewpoint suggested above. Intravenous injection of these agents probably produces an enormous increase in the number of readily accessible sites for cholesterol. Finished product is removed from the enzyme with great efficiency, and the rate of synthesis rises.

It seems possible that mechanisms akin to those outlined here may be responsible for the homeostatic control of the rate of synthesis of many bodily constituents.

We are now in a position to reexamine the relation of cholesterol metabolism to atherosclerosis. The high blood cholesterol in man may be due to an unusually large number of combining sites for cholesterol in human plasma lipoprotein. The primary cause thus becomes a species variation in protein, a chemical entity well known to vary widely from species to species. These sites are kept filled, as previously described. To return to the thermodynamic viewpoint, the activity of cholesterol is maintained at about the same level in man as in other animals, but the concentration in the blood is higher nonetheless. This picture is in accord with the well known fact that tissue concentrations of cholesterol do not show the striking species differences seen in the blood.

The interpretation presented here is only one of several which are more or less compatible with the currently available data. The possibility must also be considered that the elevated concentration of cholesterol in human serum is related to deficiencies in the mechanisms for the transfer of lipid from one lipoprotein to another. According to this view, the steady-state concentrations of cholesterol in human serum and liver would be established at values further removed from true equilibrium than in the animals with low blood cholesterols. Another reasonable interpretation of the apparent depression in cholesterol synthesis with cholesterol feeding should also be considered. As mentioned above, it is still possible that this depression will prove to be an artefact of the experimental methods, related to endogenous dilution of cholesterol precursors. If further evidence does prove that the depression is real, the cause may be adaptive reduction in enzyme concentrations, rather than a direct effect of the elevated concentration of the product of the reactions.

One might suppose that if the activity of cholesterol is the same in human serum as in the blood of other animals, the tendency of cholesterol to deposit in the arterial wall would also be the same, despite the higher concentration. A hint concerning this point may be drawn from the work of Kellner, Correll, and Ladd.[28] They found that surface-active agents offered a measure of protection against atherosclerosis in the cholesterol-fed rabbit. They found, on the other hand, that atherosclerosis could be induced by prolonged administration of the surface-active agent, even without cholesterol feeding. Apparently processes occur within the arterial wall which result in the breakdown of lipoprotein molecules which in the blood are perfectly stable. Thus, the total concentration of cholesterol in the blood may be of importance equal to or perhaps greater than the stability of the complex in which the cholesterol is held.

References

1. Bloch, K.: Biosynthesis of cholesterol. Fed. Proc. (in press).
2. Gould, R. G.: Sterol metabolism and its control. In: Symposium on Atherosclerosis. Publication 338, National Acad. of Sci. and Nat. Res. Council, Washington, D. C., 1954.
3. Werthessen, N. T.: The biosynthesis of cholesterol and its accumulation by the whole aorta maintained in vitro. Circulation, 10:594, 1954.
4. Taylor, C. B., Baldwin, D., and Hass, G. M., Localized arteriosclerotic lesions induced in the aorta of the juvenile rabbit by freezing. Arch. Path., 49: 623, 1950.
5. Waters, L. L.: The reaction of the artery wall to injury by chemicals or infection. In: Symposium on Atherosclerosis. Publication 338, National Acad. of Sci. and Nat. Res. Council, Washington, D. C., 1954.
6. Anitschkow, N., and Chalatow, S.: Uber experimentelle Cholesterinstratose und ihre Bedeutung fur die Entstehung einiger pathologischer Prozesse. Centralbl. f. allg. Path., 24:1, 1913.
7. Steiner, A., and Kendall, F.: Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil. Arch. Path., 42:433, 1946.

8. Mann, G. V.; Andrus, S. B.; McNally, A., and Stare, F. J.: Experimental atherosclerosis in Cebus monkeys. J. Exper. Med., 98:195, 1953.
9. Altschul, R.: Experimental cholesterol arteriosclerosis. Changes produced in skeletal muscle. Arch. Path., 42:277, 1946.
10. Gertler, M. M.; Garn, S. M., and Lerman, J.: The interrelationships of serum cholesterol, cholesterol esters and phospholipids in health and in coronary artery disease. Circulation, 2:205, 1950.
11. Davis, D.; Stern, B., and Lesnick, G.: The lipid and cholesterol content of the blood of patients with angina pectoris and arteriosclerosis. Ann. Int. Med., 11:354, 1937.
12. Morrison, L. M.; Hall, L., and Chaney, A. L.: Cholesterol metabolism: blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis. Am. J. M. Sci., 216:32, 1948.
13. Ahrens, E. H., and Kunkel, H. G.: The stabilization of serum lipid emulsion by serum phospholipids. J. Exper. Med., 90:409, 1949.
14. Barr, D. P.: Some chemical factors in the pathogenesis of atherosclerosis. Circulation, 8:641, 1953.
15. Gofman, J. W.; Glazier, F.; Tamplin, A.; Strisower, B., and DeLalla, O.: Lipoproteins, coronary heart disease, and atherosclerosis. Physiol. Rev., 34:589, 1954.
16. Taylor, C. B., and Gould, R. G., Effect of dietary cholesterol on rate of cholesterol synthesis in the intact animal measured by means of radioactive carbon. Circulation, 2:467, 1950.
17. Gould, R. G., and Taylor, C. B.: Effect of dietary cholesterol on hepatic cholesterol synthesis. Fed. Proc., 9:179, 1950.
18. Tomkins, G. M.; Sheppard, H., and Chaikoff, I. L.: Cholesterol synthesis by liver. III. Its regulation by ingested cholesterol. J. Biol. Chem., 201:137, 1953.
19. Langdon, R. G., and Bloch, K.: The effect of some dietary additions on the synthesis of cholesterol from acetate *in vitro*. J. Biol. Chem., 202:77, 1953.
20. Frantz, I. D., Jr.; Schneider, H. S., and Hinkelman, B. T.: Suppression of hepatic cholesterol synthesis in the rat by cholesterol feeding. J. Biol. Chem., 206:465, 1954.
21. Medes, G.; Spirtes, M. A., and Weinhouse, S.: The estimation of fatty acid synthesis in rat liver slices. J. Biol. Chem., 205:401, 1953.
22. Loud, A. V.: On the anabolic incorporation of carbon-14 and tritium into rat liver cholesterol. Ph.D. thesis, Mass. Inst. of Tech., June, 1955.
23. Fredrickson, D. S.; Loud, A. V.; Hinkelman, B. T.; Schneider, H. S., and Frantz, I. D., Jr.: The effect of ligation of the common bile duct on cholesterol synthesis in the rat. J. Exper. Med., 99:43, 1954.
24. Frantz, I. D., Jr., and Hinkelman, B. T.: Acceleration of hepatic cholesterol synthesis by Triton WR-1339. J. Exper. Med., 101:225, 1955.
25. Gould, R. G.; Campbell, D. J.; Taylor, C. B.; Kelly, F. B.; Warner, I., and Davis, C. B., Jr.: Origin of plasma cholesterol using C^{14}. Fed. Proc., 10:191, 1951.
26. Kellner, A.; Correll, J. W., and Ladd, A. T.: Sustained hyperlipemia induced in rabbits by means of intravenously injected surface-active agents. J. Exper. Med., 93:373, 1951.
27. Friedman, M., and Byers, S. O.: The mechanism responsible for the hypercholesteremia induced by Triton WR-1339. J. Exper. Med., 97:117, 1953.
28. Kellner, A.; Correll, J. W., and Ladd, A. T.: The influence of intravenously administered surface-active agents on the development of experimental atherosclerosis in rabbits. J. Exper. Med., 93:385, 1951.

CORONARY HEART DISEASE

(Continued from Page 766)

the concentration of cholesterol, especially that in the beta lipoprotein fraction of the serum, and the development of atherosclerosis.

In any case, in the effect of the mode of life must be our hope for the future. I think we can be confident that this hope is well founded.

References

Adlersberg, D.; Schaefer, L. E.; Drachman, S. D., and Dritch, R.: Circulation, 2:475, 1950.
Arnott, M.: Brit. M. J., 887 (Oct. 16) 1954.
Berkson, J.: Proc. Staff Meet. Mayo Clin., 30:319-348, 1955.
Biörck, G.; Overbeck, W., and Grönvall, C.: Cardiologia, 25:232, 1954.
Boas, E. P.; Parets, A. D., and Adlersberg, D.: Am. Heart J., 35:611, 1948.
Boissevain, E.: Engenical News, 16:115, 1931.
Doll, R., and Hill, A. B.: Brit. M. J., 1451 (June 26) 1954.
Epstein, F. H., and Boas, E. P.: J. Gerontol., 10:331, 1955.
Garn, S. M.; Gertler, M. M.; Levine, S. A., and White, P. D.: Ann. Int. Med., 34:1416, 1951.
Gertler, M M.; White, P. D., and others: Coronary heart disease in young adults. 218 pp. Cambridge, Mass.: Harvard Univ. Press, 1954.
Hammond, E. C., and Horn, D.: J.A.M.A., 155:1316, 1954.
Hobson, W.; Jordan, A., and Roseman, C.: Lancet, 961 (Nov. 7) 1953.
Keys, A.: Voeding, 13:539, 1952.
Keys, A.: J. Mt. Sinai Hosp., 20:118, 1953.
Keys, A.; Vivanco, F.; Rodriguez, Miñon, J. L.; Keys, M. H., and Castro Mendoza, H.: Metabolism, 3:195, 1954.
Keys, A.; Fidanza, F.; Scardi, V.; Keys, M. H., and di Lorenzo, F.: Arch. Int. Med., 93:328, 1954.
Keys, A.: Proc. 42nd Ann. Meeting Med. Sect. Amer. Life Convention, pp. 163-185, 1954.
Keys, A.; Anderson, J. T.; Fidanza, F.; Keys, M. H., and Swahn, B.: Clin. Chem., 1:34, 1955.
Keys, A.: J. Chronic Diseases, 1:456, 1955.
Keys, A.: In: Weight Control. Pp. 108-118. Ames, Iowa: Iowa State College Press, 1955.
Keys, A.: Am. J. Pub. Health, 44:864, 1954.
Kimura, N.: Proc. 2nd Internat. Congress Cardiol., 1955. (In press.)
Larsen, N. P.: Hawaii M. J., 14:485, 1955.
Malhotra, R. P.: Indian J. M. Sci., 5:617, 1951.
Morris, J. N., and Heady, J. A.: Brit. J. Indust. Med., 10:245, 1953.
Morris, J. N.; Heady, J. A.; Raffle, P. A. B.; Roberts, C. G., and Parks, J. W.: Lancet, 1053 and 1111 (Nov. 21 and 28) 1953.
Morris, J. N.: Proc. 2nd Internat. Congress Cardiol., 1955. (In press.)
Schornagel, H. E.: Docum. Med. Geog. Trop., 5:173, 1953.
Wilkinson, C. F., Jr.: Bull. New York Acad. Med., 26:670, 1950.

Hypertension and Atherosclerosis

LOUIS TOBIAN
Minneapolis, Minnesota

NUMEROUS studies of the relationship between hypertension and atherosclerosis have been carried out. When all the evidence is considered, it would seem that arterial hypertension does not cause atherosclerosis but will definitely accelerate it if there exists a natural underlying tendency for the process to occur. I will attempt to bring out the evidence which leads to this conclusion. Much of it is to be found in the study of atherosclerosis in the human species.

In the first place, atherosclerosis in man tends to localize in areas under increased hydrostatic pressure. As the pulse wave travels toward the bifurcation of the aorta it becomes steeper and the systolic peak is higher. The erect posture adds the weight of a column of blood to the hydrostatic pressure in the lower extremeties. This increase in pressure in the arteries of the lower part of the body is related to a much greater incidence of severe atherosclerosis in these lower arteries, necessitating the amputation of countless legs for atherosclerotic gangrene while the sacrifice of an arm for this reason is a medical rarity.[1] While atheromata are frequent in the systemic arteries, they are normally almost never found in the pulmonary artery. This protection of the pulmonary artery from atherosclerosis is due to the low pressure normally found within it. However, in patients with pulmonary hypertension, severe typical atherosclerosis may develop in the pulmonary artery. This experiment of nature is striking evidence that increased hydrostatic pressure accelerates atherosclerosis. Atheromata are also found at other loci of increased lateral pressure. For example, the knob of the transverse aorta is the target for each systolic jet from the left ventricle. At this area there is often considerable atherosclerosis, much more than is usually seen in the ascending aorta. Similarly the part of the aorta just above a coarctation often shows advanced atherosclerosis. The ventricular side of the mitral valve may show atherosclerosis. The point in the right ventricular endocardium opposite an interventricular septal defect may have an atheroma. The spot in the pulmonary artery opposite a patent ductus arteriosus may be the seat of an atheroma. The same process may be seen in a vein at the point opposite an arteriovenous fistula. Even phlebosclerosis occurs in patients with long standing elevations of peripheral venous pressure.[2] Wilens has pointed out that even cerebral atherosclerosis fits into this pattern.[1]

The second important consideration in this problem is the relationship of arterial hypertension in man to atherosclerosis. In 90 per cent of cases this means essential hypertension. At the outset it should be pointed out that there are many cases of essential hypertension without significant atherosclerosis and that there are many cases of atherosclerosis with normal arterial pressure. However, there is a considerable body of evidence that atherosclerosis is accelerated in the presence of essential hypertension.

Rosenthal studied the fat content of the aorta and found that it closely paralleled the severity of atherosclerosis. He found that patients with essential hypertension had a definitely increased fat content of the aorta for a given age compared to the general population studied.[3] Faber has made the same observation for the cholesterol content of the aorta in hypertensive patients.[4] These studies indicate an increased amount of aortic atherosclerosis in essential hypertension.

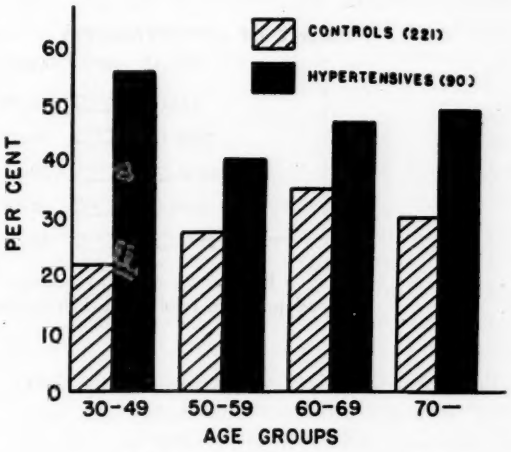
It would also appear that accelerated atherosclerosis of the renal arteries is associated with essential hypertension. Blackman found that 86 per cent of hypertensive patients had atherosclerosis of the main renal arteries, while only 10 per cent of the normotensive patients did.[5] Lisa, Eckstein, and Soloman found atheromata

From the Department of Medicine, University of Minnesota Medical School, Minneapolis.
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

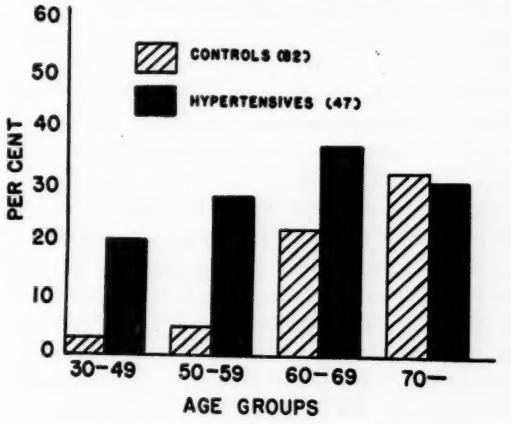
of the main renal arteries in 60 per cent of their hypertensive series and in only 43 per cent of their non-hypertensive group.[6] Richardson examined 145 consecutive autopsies; 78 per cent of the cases of essential hypertension had atheromata in the main renal arteries. Only 7 per cent of the normotensive controls had any atheromata at all in the main renal arteries, and only 3 per cent of the normotensive group had atheromatous involvement as severe as the least severe case in the hypertensive group.[7] These atheromata in the main renal artery do rarely cause hypertension in man similar to a Goldblatt experiment. In such instances there should be no arteriolosclerosis in the involved kidney. This is usually not the case in autopsy experience. In the vast majority of hypertensive patients the essential hypertension comes first and then accelerates the formation of atheromata in the main renal arteries. Usually these atheromata, even those of large size, do not significantly obstruct the lumen of the renal artery. Occasionally the atheroma is severe enough to obstruct the lumen, and in these cases there may be an aggravation of the pre-existing hypertension. However, it seems clear that hypertension does increase the frequency of atherosclerosis of the main renal arteries.

The most important problem is the influence of hypertension on coronary atherosclerosis. Bell and Clawson found severe sclerosis of the left coronary artery in 38 per cent of hypertensive patients, while only 4 per cent of a comparable normotensive control group showed similar lesions.[8]

Davis and Klainer made another well controlled autopsy study of essential hypertension and coronary sclerosis. They examined consecutive cases, utilized only blood pressure readings acquired prior to the terminal illness, and considered the factors of age and sex. They classified patients as hypertensive if the systolic pressure was consistently above 150 mm. Hg and the diastolic pressure was consistently above 90 mm. Hg. Forty-five per cent of all the hypertensive patients had severe coronary disease, compared to 27 per cent in the normotensive control patients. Figure 1 shows their comparison of hypertensives and normotensives in both sexes. In almost all age groups, the incidence of marked coronary disease is greater in the patients with hypertension. This is particularly so for patients under fifty. Hypertensive men under fifty had severe coronary disease two and one half times more frequently than their normotensive counterparts. The influence



—Marked coronary disease in males.



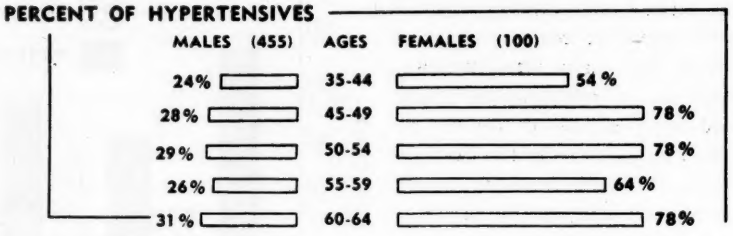
—Marked coronary disease in females.

Fig. 1.

of hypertension, however, was the most striking in women under sixty. Hypertensive women had marked coronary disease six times more frequently than the normotensive women. The incidence of marked coronary disease in hypertensive men did not increase with advancing age in this series, while the usual increase with age was seen in the normotensive group. Even though the incidence of advanced sclerosis was considerable in hypertensive women, they had about the same amount of severe coronary disease seen in normotensive men. Davis and Klainer also noted that severe elevations of blood

pressure were not associated with more coronary disease than modest elevations of pressure.[9]

In 1953, Master completed a large study relating hypertension to acute coronary occlusion.[10] This study is very pertinent to the coronary sclerosis problem since nearly all cases of coronary occlusion are related to coronary atherosclerosis. In this study the general population was grouped as to sex and age, and a pressure level two standard deviations above the mean for a given group constituted hypertension. Since the average blood pressure of the population tends to rise with age, his lower limits of hypertension correspondingly rise with age. With these criteria, 2½ per cent of any group in the general population will have hypertension. A group of 600 cases with coronary occlusion was studied; 27 per cent of all the men with coronary occlusion had hypertension by these criteria, compared to 2½ per cent in the general male population. The per cent of hypertensives in the various age groups is shown in Figure 2. The incidence of hypertension in this male group is eleven times greater than the incidence in men of the general population. Hence hypertension definitely seems to predispose to coronary occlusion in men of all age groups. A man with hypertension is thirteen times more likely to have a myocardial infarction than a normotensive man. In women, however, the influence of hypertension in promoting coronary occlusion is even greater. Seventy-one per cent of all the women with coronary occlusion had hypertension, compared to 2½ per cent hypertension in the general female population (Fig. 2). It can be estimated from these data that a woman with hypertension is eighty-five times more likely to have a coronary occlusion than a woman with normal blood pressure.



—Frequency of hypertension in 455 cases of coronary occlusion (blood pressure readings taken before the onset of coronary occlusion).

Fig. 2.

In patients with coronary occlusion, hypertension did not seem to affect the recovery from the acute attack.

Yater et al, in analyzing myocardial infarction in army men under forty, also found hypertension a predisposing factor. In the group with coronary occlusion, 19 per cent had a diastolic pressure above 90 mm. Hg, while in the control group only 3.8 per cent had a diastolic pressure above 90. Hypertension was thus five times more frequent in the coronary cases than in the controls.[11] And these figures would be even more striking in a general unselected population, since men with obvious hypertension were excluded from the army in the first place.

When Gofman et al considered the diastolic pressure as well as the lipoprotein fractions, they improved their score in predicting the presence of coronary disease.[12]

The analyses of Hunter suggest that even a "normal" blood pressure predisposes to an excessive mortality when compared to blood pressures 20 mm. lower than normal.[13]

Experiments in various animals also throw light on the relation of hypertension to atherosclerosis.

Bronte-Stewart and Heptinstall produced renal hypertension in rabbits and then fed these rabbits cholesterol. After seventy-two days of cholesterol feeding, the rabbits with high blood pressure had an average of 47 per cent of the aorta involved with atheromata, while the control rabbits with normal blood pressure had only 11 per cent of the aorta involved. The rabbits in both groups fed cholesterol had comparable elevations of serum cholesterol. Hypertension did not lead to atherosclerosis if the rabbits were not fed cholesterol. The rabbits with mild hypertension had as much aortic atherosclerosis

as the rabbits with severe hypertension. Even short periods of hypertension, such as four to five weeks markedly accelerated atheroma formation. Even in rabbits without kidney operations, increased lability of the blood pressure was associated with an increased severity of atherosclerosis.[14] Wilens noted that cholesterol fed rabbits forced to sit upright for five hours a day developed aortic atheromatosis sooner and much more extensively than control rabbits. This forced sitting produces a 40 per cent rise in arterial pressure, and the elevated pressure promptly reverts to normal when the rabbit is returned to his regular posture.[15] Evidently intermittent periods of mildly elevated blood pressure will accelerate atherosclerosis in rabbits.

The influence of DCA hypertension has also been demonstrated in cholesterol-induced atherosclerosis in chicks. Stamler, Pick and Katz found that 45 per cent of chicks receiving DCA, salt, and cholesterol had lesions in the thoracic aorta, while only 17 per cent of chicks receiving just the salt and cholesterol had thoracic atheromata.[16]

Wakerlin et al have also demonstrated an acceleration of atherosclerosis in hypertensive, hypothyroid dogs fed cholesterol. These dogs with bilateral renal artery clamps developed atherosclerosis sooner and to a much more severe degree than the normotensive control dogs.[17]

Considering all the foregoing evidence, there is little doubt that arterial hypertension accelerates atherosclerosis whenever the underlying conditions for forming atheromata are present. The mechanism of this acceleration is obscure. The most likely explanation is that the increased intraluminal pressure tends to hasten the filtration of serum lipids through the endothelial layer into the intimal space. It is also possible that the increased pressure creates an added vibration or produces some subtle mechanical damage to the artery wall with subsequent hastening of atheroma formation. More information will be needed to solve this problem.

Admitting the accelerated atherosclerosis in hypertension, what is its clinical importance? Patients with benign hypertension are endangered largely by the threat of heart failure, myocardial infarction, angina pectoris, and cerebro-vascular accidents. Myocardial infarction and angina are obviously related to coronary atherosclerosis. Moreover, angina appears in hypertensives with lesser degrees of coronary narrowing than are seen in normotensive patients with angina.[18] Moreover, congestive heart failure in hypertensive patients is often related to coronary sclerosis and thrombosis. Averbuck found that severe coronary atherosclerosis was present at necropsy in 85 per cent of patients with essential hypertension who had heart failure, but in only 10 per cent of hypertensive individuals without cardiac failure.[19] Coronary involvement, even of relatively slight degree, will diminish the very large coronary flows necessary in the hypertrophied heart of hypertensive patients. This reduction in flow retards maximum hypertrophy and promotes fibrous replacement of myocardial fibers, with the ultimate development of myocardial insufficiency. And of course gross myocardial infarction greatly hastens the onset of congestive failure. Without the accelerated atherosclerosis, essential hypertension would become a relatively benign disease.

References

1. Wilens, S. L.: Orthostatic influences on the distribution of atheromatous lesions in the cerebral and other arteries. Arch. Int. Med., 82:431, 1948.
2. Moschkowitz, E.: Vascular Sclerosis with Special Reference to Arteriosclerosis. New York: Oxford University Press, 1942.
3. Rosenthal, S. R.: Studies in atherosclerosis: chemical, experimental, and morphologic. Arch. Path., 18:660, 1934.
4. Faber, M.: The cholesterol content of the human aorta in relation to the serum cholesterol concentration. Acta med. Scandinav., 125:418, 1946.
5. Blackman, S. J.: Arteriosclerosis and partial obstruction of the main renal arteries in association with essential hypertension in man. Bull. Johns Hopkins Hosp., 65:353, 1939.
6. Lisa, J. R.; Eckstein, D., and Soloman, C.: Relationship between arteriosclerosis of the renal artery and hypertension: analysis of 100 necropsies. Am. J. M. Sci., 205:701, 1943.
7. Richardson, G. O.: Atherosclerosis of the main renal arteries in essential hypertension. J. Path. & Bact., 55:33, 1943.
8. Bell, E. T., and Clawson, B. J.: Primary (essential) hypertension: a study of four hundred and twenty cases. Arch. Path., 5:939, 1928.
9. Davis, D., and Klainer, M. J.: Hypertensive heart disease; incidence of coronary atherosclerosis in cases of essential hypertension. Am. Heart J., 19: 185, 1940.
10. Master, A.: Hypertension and coronary occlusion. Circulation, 8:170, 1953.
11. Yater, W. M.; Traum, A. H.; Brown, W. G.; Fitzgerald, R. P.; Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in men 18 to 39 years of age. Am. Heart J., 36:334, 1948.
12. Gofman, J. W.; Glazier, F.; Tamplin, A.; Strisower, B., and de Lalla, O.: Lipoproteins, coronary heart disease, and atherosclerosis. Physiol. Rev., 34:589, 1954.

(Continued on Page 793)

Hormonal Factors in the Pathogenesis of Atherosclerosis

DAVID P. BARR
New York, New York

THE following discussion is focused upon effects of hormones on concentration and distribution of lipids in plasma. Its relevance to the pathogenesis of atherosclerosis is based on assumption that lipid composition of plasma exerts an influence on the rate of development of atherosclerosis and its complications.

Most of the discussion is centered about observations made by Miss Ella Russ, Dr. Howard Eder, and myself at the New York Hospital-Cornell University Medical Center. Chief emphasis is placed on the relative concentration of alpha and beta lipoproteins and the manner in which cholesterol is distributed between them. This relationship is stressed because previous experience in study of many conditions of varying degree of atherogenicity has indicated that it correlates more accurately than others with tendency to atherosclerosis.[1,2,3] For convenience of presentation this relationship is usually expressed as the percentage of total cholesterol combined with alpha lipoproteins.

Action of Gonadal Hormones

The most convincing evidence of hormonal influence on lipid composition of plasma has been obtained by study of action of estrogens and androgens.

Administration of estrogens to men who have survived one or more attacks of myocardial infarction accomplishes several predictable actions, with the result that the gross abnormalities in lipids usually found in these atherosclerotic men are almost completely corrected.[4] The most constant effect is an increase in concentration of alpha lipoproteins and a corresponding decrease in concentration of beta lipoproteins. Usually there is also a considerable reduction in concentration of cholesterol and almost always a sharp reduction in cholesterol-phospholipid ratios of plasma and of beta lipoproteins. Direction and extent of these changes are indicated in Table I.

TABLE I. EFFECT OF ESTROGENS ON CONCENTRATION AND DISTRIBUTION OF LIPIDS

Conditions	Total Cholesterol Mg. per 100 Ml.	Cholesterol in Form of Alpha Lipoproteins		Cholesterol in Form of Beta Lipoproteins	Cholesterol-Phospholipid Ratio by Weight	
		Mg. per 100 Ml.	% of Total	Mg. per 100 Ml.	Plasma	Beta Lipoproteins
Before estrogen	282	32	11.3	250	1.05	1.32
After 9 weeks of estrogen	210	57	27.1	153	0.72	0.97
2 weeks after withdrawal	285	53	18.5	220		

More recent observations in our laboratory have shown that in women who have suffered myocardial infarction action of estrogen is similar in direction and extent to that observed in men. In the women a daily dose of 1.0 mg. of estinyl was maintained continuously with addition of 100 mg. of pranone for each of four days at the end of each month. Effects of treatment are indicated in Table II.

In cases of familial hypercholesterolemia and xanthomatosis with their extreme atherogenic tendency, effects of estrogens are similar in direction but seldom are sufficient to accomplish complete restoration of normal conditions. In the atherogenic state of nephrosis fragmentary and insufficient observations have offered little

From the Department of Medicine, New York Hospital-Cornell Medical Center, New York, New York.
Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

hope that estrogens will alter beneficially the extreme lipid abnormalities.[4]

In hypothyroidism which has often been regarded as atherogenic there is some evidence that estrogen may alter or correct abnormalities in lipid composition of plasma. Observations recorded in Table III were made on plasma of a forty-eight-year-old cretin whose basal metabolic rate during period of treatment with estrogen was -26.

Effects of androgens on the lipid composition of plasma are in general the exact opposite to those following use of estrogens.[4] They exaggerate chemical pathology of survivors of myocardial infarction and produce abnormalities in plasma of individuals whose protein-lipid patterns previously have been normal. A constant effect of administration of methyl testosterone is relative increase in concentration of beta lipoproteins and a corresponding decrease in concentration of alpha lipoproteins. In some individuals there is also augmentation of concentration of cholesterol in unfractionated plasma with increase in cholesterol-phospholipid ratios of plasma and of beta lipoproteins. The changes in relative concentrations of alpha and beta lipoproteins expressed as percentage of cholesterol in alpha lipoproteins is presented in Table IV.

When estrogens and androgens are given simultaneously, effects of estrogens are modified or obliterated.[4] An example illustrating the extent of neutralization accomplished by methyl testosterone in daily doses of 50 mg. may be seen in Table V. Similar neutralization has been

TABLE II. EFFECT OF ESTROGEN THERAPY IN MYOCARDIAL INFARCTION OF WOMEN

Patient	Age	Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in Alpha Lipoprotein	Cholesterol in Beta Lipoprotein Mg./100 Ml.	Cholesterol-Phospholipid Ratio	
						Plasma	Beta Lipoprotein
Bie	46	Before estrogen	342	12.4	297	1.03	1.26
		After 84 days 10,000 r.u. estinyl o.d.	211	36.6	132	0.67	0.94
Cha	59	Before estrogen	368	20.3	288	0.93	1.29
		After 41 days 10,000 r.u. estinyl o.d.	313	29.8	213	0.82	1.27
Coh	44	Before estrogen	358	10.2	316	1.19	1.34
		After 54 days 10,000 r.u. estinyl o.d.	313	22.7	234	0.91	1.33
Wol	48	Before estrogen	411	8.5	369		
		After 5 months 10,000 r.u. estinyl o.d.	337	19.8	265		
		2 months after withdrawal	441	9.8	362		

TABLE III. EFFECT OF ESTROGEN THERAPY IN CRETINISM

Name	Age	Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol in Alpha Lipoprotein	Cholesterol in Beta Lipoprotein Mg./100 Ml.	Cholesterol-Phospholipid Ratio	
						Plasma	Beta Lipoprotein
Laz	58	Before estrogen	374	11.3	330	1.10	1.40
		After 22 days 10,000 r.u. estinyl o.d.	301	21.3	232	0.91	1.20
		2 months after withdrawal	391	10.8	343	1.17	1.35
		After 27 days 10,000 r.u. estinyl o.d.	260	25.4	189	0.68	0.97

TABLE IV. EFFECTS OF METHYL TESTOSTERONE ON CONCENTRATION AND DISTRIBUTION OF LIPIDS

Conditions	Percentage of Total Cholesterol in Alpha Lipoprotein
Before testosterone	22.8
After testosterone	14.4
After withdrawal of testosterone	22.1

observed from use of 5 to 10 mg. methyl testosterone each day.

Observations on use of gonadal hormones show that protein-lipid patterns of plasma can

TABLE V. INFLUENCE OF COMBINED ESTROGEN AND METHYL TESTOSTERONE

Conditions	Total Cholesterol Mg./100 Ml.	Percentage of Cholesterol in Form of Alpha Lipoproteins	Cholesterol in Form of Beta Lipoproteins Mg./100 Ml.
Before use of hormone	202	9.7	171
After 5 days 10,000 r.u. estinyl o.d.	173	29.6	120
After 69 days 5,000 r.u. estinyl o.d.	194	33.1	130
After 56 days 2,500 r.u. estinyl o.d.	217	31.2	148
After 28 days combined dosage 2,500 r.u. estinyl & 50 mg. methyl testosterone o.d.	351	3.2	338
After 50 days 2,500 r.u. estinyl o.d. without methyl testosterone	226	27.6	161

be radically modified. They seem to have some relevance to the pathogenesis of atherosclerosis since they indicate a chemical reason for the relative immunity of young women to the complications of atherosclerosis and the greater susceptibility of young men to these accidents. They suggest that action of estrogenic substances in persons exhibiting the protein-lipid abnormalities of the type characteristic of atherogenesis might be beneficial and that use of methyl testosterone in such patients might be harmful.

Action of Thyroid Hormones

Effects of thyroid hormones on concentration and distribution of lipoproteins and on pathogenesis of atherosclerosis are of special interest because of the well-known influence of thyroid activity on the concentration of cholesterol and phospholipids.[5] The question may be studied by examination of lipid composition of plasma in states of hyper- and hypothyroidism or during alteration of pathologic conditions by therapy. Table VI contains observations on plasma of a few patients with Graves' disease.

In this small group of patients ranging in age from thirty-four to sixty-nine, the low normal concentration of cholesterol is apparent. The average of 145 mg. per 100 ml. may be compared with a normal of 190 for young men and women, and of 245 for presumably normal older persons. Emphasis on this aspect is unnecessary, however, since there is in the literature abundant evidence that hyperthyroidism tends to reduce the level of plasma cholesterol. Attention is called especially to the percentages of total cholesterol in alpha lipoproteins where

TABLE VI. CONCENTRATION AND DISTRIBUTION OF CHOLESTEROL IN THYROTOXICOSIS

Sex	Age	Total Cholesterol Mg./100 Ml.	Percentage Total Cholesterol in Alpha Lipoproteins
M	34	158	21.1
M	36	168	16.0
M	53	125	38.0
M	48	153	27.8
M	59	165	32.3
M	63	135	17.9
M	69	111	34.9
F	66	150	31.1
F	44	146	27.5
F	54	142	24.4

the values reveal no trend. It is perhaps noteworthy that two of the patients, one of whom is only thirty-six years of age, show distribution of cholesterol possibly indicative of an atherogenic tendency.

In Table VII results of treatment in Graves' disease and myxedema are presented. In each of the patients with Graves' disease treatment with antithyroid drugs or radioactive iodin resulted in marked increase in the level of plasma cholesterol. In two of them there was also a considerable reduction in the percentage of total cholesterol in the form of alpha lipoproteins. In the other three the percentage in alpha lipoprotein was actually increased. Again, no trend is apparent. In the cases of myxedema there was in each instance with treatment an increase in basal metabolic rate or a reduction in concentration of plasma cholesterol or both. On the other hand, the changes in the percentage of total cholesterol in the form of alpha lipoprotein were trivial and not always in the same direction. It is also of some interest that those patients whose percentage in alpha lipoprotein was initially low tended to maintain a low presumably atherogenic level after treatment.

Failure to demonstrate effect of thyroid hormones on distribution of cholesterol between alpha and beta lipoprotein is also apparent in the observation on the action of intravenously-injected tri-iodo-thyronine which is presented in Table VIII.

Although both basal metabolic rate and cholesterol concentrations were considerably modi-

fied by the action of the hormones, changes in the percentage of total cholesterol in alpha lipoproteins were trivial.

These observations are of some interest in relation to clinical thought concerning the relationship of thyroid activity to the pathogenesis of atherosclerosis. Although there is abundant evidence that thyrotoxic individuals tend to have relatively low concentrations of cholesterol, there is no anatomic evidence that such patients have less than usual tendency to atheromatous deposits in arteries. Myxedema has often been listed as one of the diseases in which atherosclerosis develops extensively and prematurely. This impression has received some support from an apparently high incidence of myocardial infarction in hypothyroid patients and because of a long-prevalent idea that patients with higher than normal concentrations of cholesterol have a greater than usual tendency to develop coronary disease. There is no sound anatomic evidence that myxedematous patients have more atheromatous deposit than others of the same age in the general population. Indeed, Blumgart's study[6] of patients subjected to complete thyroidectomy revealed no greater than ordinary atheromatous deposits in large vessels.

TABLE VII. EFFECT OF THYROID ACTIVITY ON CONCENTRATION AND DISTRIBUTION OF LIPIDS

Diagnosis	Sex	Age	Conditions	Basal Metabolic Rate	Cholesterol Mg./100 Ml.	Percentage of Total Cholesterol Alpha Lipoprotein
Graves' Disease	M	34	Before treatment	+47	158	21.1
			After 5 months	+39	375	10.6
Graves' Disease	M	69	Before treatment	+36	111	34.9
			After 3 months	−24	260	23.7
Graves' Disease	M	36	Before treatment	+23	168	16.0
			After 3 weeks	−10	281	17.9
Graves' Disease	M	48	Before treatment	+22	153	27.8
			After 2½ months		264	31.4
Graves' Disease	F	66	Before treatment	+16	150	31.1
			After 2 weeks	+ 1	218	36.9
Myxedema	M	60	Before treatment	−31	391	12.6
			After 6 weeks	−18	191	16.6
Myxedema	M	50	Before treatment	−35	346	12.8
			After 6 months	−24	360	11.3
Myxedema	F	37	Before treatment	−41	380	13.3
			After 3 months	−19	300	11.5
Myxedema	F	46	Before treatment	−26	272	23.7
			After 6 months	+ 9	133	21.6

Action of Cortisone

Extensive observations by Adlersberg and his associates[7,8] have indicated that cortisone administration in a variety of clinical states is followed by increased concentrations of serum cholesterol. Although this is not invariable it has averaged about 20 per cent. In some patients the augmentation of serum cholesterol became apparent in two weeks, while in others it required two or three months. The effect was both greater and prompter in patients with initially high serum cholesterol.

TABLE VIII. EFFECT OF TRI-IODO-THYRONINE DISTRIBUTION AND CONCENTRATION OF LIPIDS

Day	Basal Metabolic Rate	Cholesterol Mg./100 Ml.	Percentage Total Cholesterol in Alpha Lipoproteins
May 11	−38	456	6.9
May 12	−38		
10 a.m. 1.0 mg. Tri-iodo-thyronine i.v.			
May 13	−14	388	9.2
May 18	−16	338	8.4
May 27	−35		
June 1		357	12.8

Our own studies have been limited and are mentioned only because the Cohn method of fractionation gives some insight concerning the concentration of alpha and beta lipoproteins and the distribution of cholesterol between them. In Table IX observations on six normal men and four normal women are presented. Blood was drawn for microfractionation before treatment was started; again, after several days' cortisone administration.

Changes are not impressive. No increase in concentration of cholesterol is apparent. Slight increase in the percentage of cholesterol in alpha lipoproteins, notable in six of ten cases, does not obviously depend on size of dose of cortisone.

Some observations on use of cortisone in pathologic states are presented in Table X. They have been selected as illustrative of the variability of results and of difficulty in evaluating cortisone for five days shows no significant change in concentration or distribution of cholesterol. Later, a dose of 400 mg. three times each week is followed after fifty days by com-

TABLE IX. EFFECT OF CORTISONE NORMAL MEN AND WOMEN

Subject	Sex	Age	Daily Dose Mg.	Conditions	Cholesterol Mg./100 Ml.	Percentage Total Cholesterol in Alpha Lipoproteins
Sc.	M	25	25	Before	206	17.4
				After 5 days	208	16.8
Eh.	M	40	50	Before	205	21.2
				After 5 days	184	28.2
Ho.	M	28	100	Before	249	15.7
				After 5 days	257	17.8
Ed.	M	37	100	Before	178	18.3
				After 7 days	188	24.4
Ba.	M	64	100	Before	233	26.2
				After 7 days	211	36.3
Li.	M	30	150	Before	238	22.4
				After 5 days	212	20.7
Ca.	F	40	100	Before	201	21.2
				After 5 days	184	28.2
Vo.	F	28	100	Before	179	36.2
				After 5 days	185	34.4
Da.	F	28	100	Before	239	35.1
				After 5 days	228	34.2
Ru.	F	38	100	Before	156	24.5
				After 14 days	137	31.4
Average				Before	208	23.8
				After	199	27.2

TABLE X. EFFECT OF CORTISONE IN DISEASE

Sex	Age	Clinical State	Daily Dose Mg.	Duration of Treatment	Cholesterol Mg./100 Ml.		Per Cent Cholesterol Alpha Lipoprotein	
					Before	After	Before	After
F	13	Asthma		14 days	135	181	36.5	37.5
				28 days		194		43.2
F	55	Muscular Dystrophy	100	10 days	193	116	28.8	31.4
F	19	Nephrotic Syndrome	400	14 days	394	472	8.8	7.9
				34 days		537		7.9
				54 days		624		9.4
M	25	Nephrotic Syndrome	500	5 days	711	737	2.5	3.7
			400	10 days	398	513	8.8	9.8
				25 days		438		9.8
				44 days		294		13.4
				50 days		247		17.7
M	61	Hypopituitarism	100	14 days	194	233	21.3	23.5
M	64	Hypopituitarism	100	14 days	249	324	26.1	26.1

hormonal effects in the changing background of active disease. In the girl with asthma, increased cholesterol concentration apparent after seven days and persistent at the end of two weeks of treatment is accompanied by significant increase in percentage of cholesterol in alpha lipoprotein. A menopausal, dystrophic woman of fifty-five exhibits after ten days a sharp reduction in cholesterol concentration with slight change in distribution of cholesterol. The young woman with nephrotic syndrome shows progressive increase in cholesterol concentration with no considerable change in distribution of cholesterol. The nephrotic young man on 500 mg. of plete chemical remission. In each of two cases of hypopituitarism in elderly men, cholesterol concentration increases without significant change in distribution.

Variable and inconstant effects of cortisone are in sharp contrast to predictable changes observed following administration of gonadal hormones.

Relationship of adrenal cortical hormones to development of atherosclerosis depends on somewhat questionable circumstantial evidence. On basis of clinical impression, it has been assumed that Cushing's syndrome and adrenal hyperfunction exert an atherogenic influence. Similarly

without statistical proof it has been stated that patients with Addison's disease have a less than usual degree of atherosclerosis. The most direct evidence concerning the influence of adrenal cortical hormones on the development of lipid deposit in vessels comes from a study of Etheridge and Hoch-Ligeti,[9] who found that children between the ages of one and ten who had received large amounts of cortisone or ACTH had a greater degree of lipid deposit in vessels than did untreated patients with similar disease. This interesting study was somewhat less than decisive because of the necessity of the use of other therapeutic agents in the patients under consideration. Observations by Adlersberg and his associates[10] and by Gordon, Kobernick, McMillan, and Duff[11] indicate that use of cortisone in rabbits fed large amounts of cholesterol actually diminishes the degree of atherosclerosis.

Summary

Our observations indicate that the use of gonadal hormones both estrogenic and androgenic exert predictable effect on relative concentration of alpha and beta lipoproteins and on distribution of cholesterol between them. Lack of thyroid hormone permits accumulation of cholesterol, while excess of the hormone leads to lowering of concentration of cholesterol in plasma. Neither lack nor excess of thyroid hormone causes predictable changes in the relative concentration of alpha and beta lipoproteins. Administration of cortisone is followed by variable changes in concentration of cholesterol. It is not established that use of cortisone leads to predictable alteration in relative concentrations of alpha and beta lipoproteins.

The changes observed following use of estrogens and androgens appear to have some possible correlation with pathogenesis of atherosclerosis. A similar relationship has not been demonstrated for thyroid or adrenal hormones.

References

1. Russ, E. M.; Eder, H. A., and Barr, D. P.: Protein-lipid relationships in human plasma. I. In normal individuals. Am. J. Med., 11:468, 1951.
2. Barr, D. P.; Russ, E. M., and Eder, H. A.: Protein-lipid relationships in human plasma. II. In atherosclerosis and related conditions. Am. J. Med., 11:480, 1951.
3. Barr, D. P.: Some chemical factors in the pathogenesis of atherosclerosis. Circulation, 8:641, 1953.
4. Russ, E. M.; Eder, H. A., and Barr, D. P.: Influence of gonadal hormones on protein-lipid relationships in human plasma. Am. J. Med., 19:4, 1955.
5. Peters, J. P., and Man, E. B.: The significance of serum cholesterol in thyroid disease. J. Clin. Investigation, 29:1, 1950.
6. Blumgart, H. L.; Freedberg, A. S., and Kurland, G. S.: Hypercholesterolemia, myxedema and atherosclerosis. Tr. A. Am. Physicians, 65:114, 1952.
7. Adlersberg, D.; Schaefer, L., and Drachman, D. R.: Development of hypercholesteremia during cortisone and ACTH therapy. J. A. M. A., 144:909, 1950.
8. Adlersberg, D.; Schaefer, L. E., and Drachman, S. R.: Studies on hormonal control of serum lipid partition in man. J. Clin. Endocrinol., 11:67, 1951.
9. Etheridge, E. M., and Hoch-Ligeti, C.: Lipid deposition in aortas in younger age groups following cortisone and adrenocorticotrophic hormone. Am. J. Path., 28:315, 1952.
10. Adlersberg, D.; Schaefer, L. E., and Wang, Chun-I: Adrenal cortex, lipid metabolism and atherosclerosis: Experimental studies in the rabbit. Science, 120: 319, 1954.
11. Gordon, D.; Kobernick, S. D.; McMullan, G. C., and Duff, G. L.: The effect of cortisone on the serum lipids and on the development of experimental cholesterol atherosclerosis in the rabbit. J. Exper. Med., 99:371, 1954.

HYPERTENSION AND ATHEROSCLEROSIS

(Continued from Page 787)

13. Hunter, A.: Blood pressure among standard lives. J. Inst. Actuaries, 70:60, 1939.
14. Bronte-Stewart, B., and Heptinstall, R. H.: The relationship between experimental hypertension and cholesterol-induced atheroma in rabbits. J. Path. & Bact., 68:407, 1954.
15. Wilens, S. L.: The effect of postural hypertension on the development of atheromatosis in rabbits fed cholesterol. Am. J. Path., 19:293, 1943.
16. Stamler, J.; Pick, R., and Katz, L. N.: Effect of desoxycorticosterone acetate on cholesterolemia, blood pressure, and atherogenesis in chicks. Circulation, 4:262, 1951.
17. Wakerlin, G. E.; Moss, W. G.; Neville, J. B., and Bourque, J. E.: The effect of experimental renal hypertension on experimental cholesterol atherosclerosis in factors regulating blood pressure. Tr. Fifth Conference, New York, p. 193, Josiah Macy, Jr. Foundation, 1951.
18. Davis, D., and Klainer, M. J.: Hypertensive heart disease; factors in production of angina pectoris. Am. Heart J., 19:198, 1940.
19. Averbuck, S. H.: Heart failure in hypertension. Am. Heart J., 11:99, 1936.

Coronary Atherogenesis—An Endocrine Problem?

M. F. OLIVER and G. S. BOYD
Edinburgh, Scotland

IT is well recognized that there is a remarkable sex difference in the incidence of coronary disease. A recent analysis of 1,000 consecutive cases attending the Edinburgh Royal Infirmary, all of whom had electrocardiographic evidence of myocardial infarction or ischemia, indicated that the clinical manifestations of coronary disease were nineteen times more common in men than in women under the age of thirty-five, and fifteen times more common under the age of forty (Table I). This striking sex difference in the incidence of the overt disease is probably not true for atheromatous lesions of the coronary arteries (Lober, 1953), and this suggests that women are protected in some way from the development of the clinical manifestations of coronary disease so long as their reproductive physiology is maintained. The increase in the incidence of the disease after a natural menopause, and prematurely following an artificial menopause, presumes that its development may be accelerated by changes in the hormonal equilibrium. The continuation of this sex difference into the seventh decade suggests that middle-aged men may be exposed more than middle-aged women to pathogenetic factors which favour rapid evolution of the disease.

In contrast, there has been no significant difference between the sexes in the increase in the morbidity and mortality rates either from coronary disease or from cerebral vascular disease during the last two decades (Fig. 1). The morbidity figures represent the number of patients diagnosed annually as suffering from coronary disease and from cerebral vascular disease in the medical wards of the Edinburgh Royal Infirmary; the total admissions to these wards for all causes averaged 6,000 annually. The mortality figures represent the number of subjects certified annually as dying from coronary disease and from cerebral vascular disease in Scotland; the total number of deaths from all causes averaged 64,000 annually. When the morbidity and mortality rates were each expressed as a percentage rise over the 1937 figures, there was no significant difference between them and thus for this analysis they have been combined. Since 1937 the incidence of coronary disease has increased five times compared with an increase in the incidence of cerebral vascular disease of less than twice. A similar increase in coronary disease has been reported from many civilized countries and, despite the better diagnosis, the aging population and the greater interest of the last twenty years, there has probably been a real rise in the incidence of the disease.

TABLE I. SEX AND AGE DISTRIBUTION OF 1000 CONSECUTIVE CASES OF CORONARY DISEASE ATTENDING EDINBURGH ROYAL INFIRMARY.

	Numbers of Cases		Ratio of Men to Women
	Men	Women	
Younger than 35	19	1	19:1
35-39	44	3	15:1
40-49	188	26	7:1
50-59	256	53	5:1
60-69	195	86	2:1
Older than 70	68	61	1:1

The distinction between the incidence of the clinical manifestations of coronary disease and those of cerebral vascular disease is interesting. Whether thrombosis or a disturbance of lipid metabolism is of greater importance in the genesis of atherosclerosis the selective involvement of the coronary arteries must be explained. The dynamic and morphological characteristics of the coronary circulation may alone be sufficiently different from those of the cerebral circulation to account for this selectivity, but it may also be significant that no abnormalities in the circulating lipids and lipoproteins have yet been

From the Department of Cardiology, Royal Infirmary, Edinburgh and the Department of Biochemistry, University of Edinburgh.

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

established in cerebral vascular disease when it is dissociated, which is often difficult, from coronary disease. In contrast, clinical coronary disease is commonly associated with abnormal

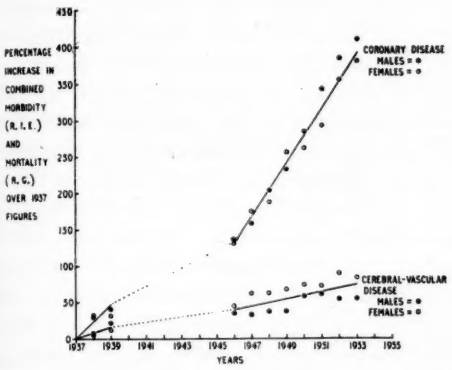


Fig. 1. The percentage increase in the combined morbidity and mortality rates for coronary disease and for cerebral vascular disease over the 1937 figures. The morbidity rates were obtained from hospital admissions (Royal Infirmary, Edinburgh) and the mortality rates from certification in Scotland (Registrar-General's Report). The dotted lines represent the war years during which accurate analyses of morbidity and mortality rates was not possible as part of the hospital was occupied by troops and the wartime population of Scotland was not static or comparable to the peacetime population.

circulating lipids and lipoproteins. In Britain a controlled investigation of subjects with coronary disease has indicated that there is elevation of the plasma total cholesterol, of the plasma total-cholesterol : phospholipid ratio (the C/P ratio) and of the concentration of cholesterol attached to the β lipoprotein fraction, as determined by paper electrophoresis, and thus a low $\alpha:\beta$ lipoprotein ratio (Oliver and Boyd, 1953b, 1955b). These abnormalities are comparable to those observed in the United States (Gertler et al, 1950; Barr et al, 1951; Steiner et al, 1952; Rosenberg et al, 1954).

The apparent protection of premenopausal women from clinical coronary disease and the particular association of coronary disease with abnormal circulating lipids and lipoproteins both emphasize the importance of hormonal and metabolic factors in the etiology of the disease. Study of the circulating lipids and lipoproteins during the menstrual cycle and pregnancy, the two physiological states peculiar to premenopausal women, has focussed attention on the endocrine aspects of coronary atherogenesis.

Menstrual Cycle

The plasma total cholesterol and the C/P ratio were both depressed at ovulation in each of twelve young nulliparous women whose cir-

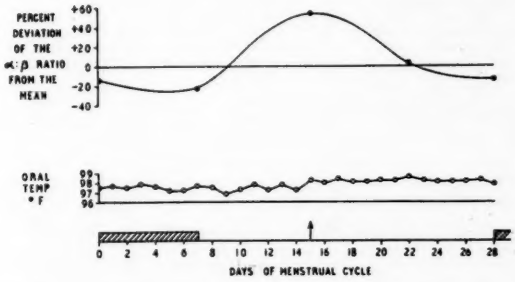


Fig. 2. The percentage deviation of the $\alpha:\beta$ lipoprotein ratio from its mean during the menstrual cycle of a typical healthy nulliparous woman, aged 30 years. Ovulation was determined by a rise at the mid-point of the cycle in the early morning oral temperature.

culating lipids were estimated during their menstrual cycles (Oliver and Boyd, 1953a). No such cyclical changes were observed in a group of twelve young men in whom analyses were made twice weekly for five weeks. In another group of twelve normal young women the distribution of cholesterol between the α and β lipoprotein fractions varied during the menstrual cycle (Oliver and Boyd, 1956b). There was less cholesterol attached to the β lipoprotein fraction, and thus a higher $\alpha:\beta$ ratio, at ovulation than at any other time during the cycle (Fig. 2). The relative concentrations of the ovarian hormones during the menstrual cycle are of interest in view of these cyclical changes. The secretion of the estrogenic hormones is maximal immediately before ovulation and remains high throughout the luteal phase (Smith and Smith, 1936; Brown, 1955); the peak coincides with the time when the plasma cholesterol, the C/P ratio and the concentration of cholesterol on the β lipoprotein fraction are all lowest. These values, therefore, may undergo regular variation in women during their reproductive years partly as a result of the endogenous secretion of estrogenic hormones at the midpoint and during the luteal phase of the cycle. These cyclical changes should be taken into consideration when making comparative studies of the circulating lipids and lipoproteins in young women, and the sex differences in lipid and lipoprotein con-

TABLE II. CHANGES IN THE CIRCULATING LIPIDS AND LIPOPROTEINS AFTER SIX MONTHS STUDY OF 40 MEN WITH CORONARY DISEASE.

	Plasma Total Cholesterol mg%.	Plasma C/P Ratio	Serum α:β Ratio
Ethinyl Estradiol (20 men)			
(a) Mean control value.	251	1.01	9:91
(b) 6 months later.	223	0.74	18:82
Inert Tablets (20 men)			
(a) Mean control value.	236	0.95	10:90
(b) 6 months later.	230	0.93	9:91

centrations, which have been reported in young subjects (Russ et al, 1951; Jones et al, 1951; Nikkila, 1953; Antonini, 1953), may partly result from the physiological variation within a menstrual cycle.

Pregnancy and the Puerperium

The circulating lipid and lipoprotein concentrations have been studied serially throughout pregnancy in twelve young healthy women (Oliver and Boyd, 1955a). As pregnancy advanced there was a gradual rise in the plasma cholesterol, the C/P ratio and the concentration of cholesterol on the β lipoprotein fraction, and by the thirty-second week the levels and distribution of the lipids and lipoproteins in each woman resembled those seen in the presence of clinical coronary disease; subsequently they regressed to return almost to the resting values by the fifth postpartum month. The development of a "coronary pattern" is fascinating particularly as clinical coronary disease is so rare during pregnancy. The relationship of multiple pregnancies to the subsequent development of clinical coronary disease is being studied, and preliminary observations from 500 postmenopausal women with coronary disease and 500 healthy women of comparable age indicates that the number of pregnancies in the former group is just significantly greater than in the healthy group. This investigation may help to assess the importance of episodes of hypercholesterolemia in the genesis of coronary atherosclerosis. The hypercholesterolemia of pregnancy is difficult to understand as there is an enormous increase in the concentration of circulating estrogens, increased thyroid and also increased adrenal activity—all of which are associated with a hypocholesterolemic response in men with coronary disease.

Estrogens

Correlation of the cyclical changes in the circulating lipids and lipoproteins during the menstrual cycle with endogenous estrogen secretion suggested that the administration of estrogens might influence the abnormal circulating lipids and lipoproteins of clinical coronary disease. A small pilot study indicated that a daily dose of 200 μg. or more of ethinyl estradiol caused depression of the plasma cholesterol, the C/P ratio and the concentration of cholesterol on the β lipoprotein fraction (Oliver and Boyd, 1954). Subsequently, ethinyl estradiol has been administered to more than 100 men with electrocardiographic evidence of myocardial infarction or ischemia and every man has shown some depression of these values (Oliver and Boyd, 1956a). Comparative studies of the effect of different strengths of ethinyl estradiol suggested that a dose larger than 200 μg. was not more effective in depressing the circulating lipids and might be a disadvantage in that it was more readily associated with feminizing side effects. Generally it is our experience that the higher the plasma cholesterol, the C/P ratio and the concentration of cholesterol attached to β lipoprotein fraction, the greater is the depressant action of ethinyl estradiol; it is upon the cholesterol increment present in coronary disease that ethinyl estradiol is most effective. Ethinyl estradiol was the only estrogen which caused highly significant depression of these values, although hexestrol and estradiol produced a similar trend. Estrone and estriol failed to produce any significant alteration in these values when administered in doses of equivalent estrogenic potency.

It is fundamental to determine whether control of the abnormal circulating lipid and lipoprotein patterns will inhibit or even cause regression of atherosclerotic lesions. Retardation of the atherosclerotic process once a myocardial infarct has developed may not necessarily prolong life. It is, therefore, essential to assess the effect of estrogens in terms of morbidity and mortality and thus a long-term study on men recovering from their first myocardial infarct was started in Edinburgh two years ago. Alternate cases have received either 200 μg. of ethinyl estradiol daily or identical inert tablets; there are now thirty-five men in each group. It is yet too early to make any significant ob-

servation on improvement or worsening of the functional capacity, on the morbidity rate or on the mortality rate of the two groups, but the change after six months in the lipids and lipoproteins in the first forty men is shown in Table II. Ethinyl estradiol at a dose of 200 μg. daily has been remarkably well tolerated; the majority of men developed gynecomastia and experienced depression or loss of libido, but these feminizing effects have never been severe enough to require withdrawal of the estrogen and are not regarded as major obstacles to the administration of ethinyl estradiol *at this dose level.*

Androgens

Methyl testosterone 50 mg. daily for ten days resulted in a significant increase in the concentration of cholesterol on the β lipoprotein fraction in six men who had had a myocardial infarct; there was no change in the effort tolerance of these men.

In an attempt to overcome some of the feminizing effects of estrogen therapy, methyl testosterone was administered simultaneously to two groups of hypercholesterolemic men with coronary disease. At the levels of 10 and 20 mg. daily, methyl testosterone caused partial inhibition of the depressant action of ethinyl estradiol on the circulating lipids and lipoproteins and failed to ameliorate any of the feminizing effects. The action of methyl testosterone on the circulating lipids and lipoproteins was most striking when ethinyl estradiol had been administered and its effect was being antagonized.

Our experiences with estrogens and androgens, which will shortly be reported in detail (Oliver and Boyd, 1956a), are very much in agreement with those recently published by Russ, Eder and Barr (1955).

Progestins

The intramuscular administration of pure progesterone 100 mg. daily for five days produced no significant change in the circulating lipids and lipoproteins of six hypercholesterolemic men with coronary disease.

A further attempt to eliminate the feminizing effects of estrogen therapy was made by the simultaneous administration of a progesterone analogue to twelve hypercholesterolemic men with coronary disease. This analogue, ethinyl testosterone, did not relieve the feminizing effects and did not have any significant action on the circulating lipids and lipoproteins when administered at a level of 60 mg. daily.

TABLE III. CHANGES IN THE CIRCULATING LIPIDS AND LIPOPROTEINS IN 6 HYPERCHOLESTEROLEMIC MEN WITH CORONARY DISEASE WHEN ACTH WAS ADMINISTERED.

	Plasma Total Cholesterol mg%.	Plasma C/P Ratio	Serum α:β Ratio
Before ACTH	268	1.00	9:91
After ACTH	224	0.84	17:83
10 weeks later	260	1.03	6:94

TABLE IV. CHANGES IN THE CIRCULATING LIPIDS AND LIPOPROTEINS IN 6 HYPERCHOLESTEROLEMIC MEN WITH CORONARY DISEASE WHEN CORTISONE ACETATE WAS ADMINISTERED.

	Plasma Total Cholesterol mg%.	Plasma C/P Ratio	Serum α:β Ratio
Before Cortisone	282	1.05	11:89
After Cortisone	223	0.89	16:84
10 weeks later	249	0.96	12:88

Pituitary-Adrenal Axis

Certain clinical endocrine disorders, such as diabetes, myxedema and Cushing's disease, may be associated with the complications of atherosclerosis, and, as most metabolic processes are affected by several hormones, it is unlikely that the circulating lipids and lipoproteins are influenced only by the sex hormones. It is interesting, therefore, to consider some preliminary observations concerning the effects of other hormones on the circulating lipids and lipoproteins of hypercholesterolemic men with a previous myocardial infarct.

There have been few and conflicting reports concerning the effect of ACTH and cortisone on the circulating lipids and lipoproteins in the human (Conn et al, 1950; Adlersberg et al, 1951; Mann and White, 1953).

The intramuscular administration of ACTH-Gel 100 mg. daily for five days to six men resulted in significant depression of plasma total cholesterol, the C/P ratio and the concentration of cholesterol attached to the β lipoprotein fraction (Table III). The administration of cortisone acetate 100 mg. daily for ten days to six other men also resulted in significant depression of these values (Table IV). There was no change in the functional capacity or the

TABLE V. CHANGES IN THE CIRCULATING LIPIDS AND LIPOPROTEINS IN 6 HYPERCHOLESTEROLEMIC MEN WITH CORONARY DISEASE WHEN L-THYROXINE SODIUM WAS ADMINISTERED.

	Plasma Total Cholesterol mg%.	Plasma C/P Ratio	Serum α:β Ratio
Before Thyroxine	274	1.03	12:88
After Thyroxine	200	0.85	12:88
6 weeks later	270	0.96	12:88

frequency of anginal attacks in any of these men during or after treatment.

The intramuscular administration of desoxycortone acetate 15 mg. daily for five days to three men did not result in any significant change in the circulating lipids and lipoproteins.

Pituitary-Thyroid Axis

Thyroid stimulating hormone has not yet been administered to hypercholesterolemic men with coronary disease. The intramuscular administration of TSH 10 units daily for four days to three subjects with primary myxedema did not result in any significant alteration in the circulating lipids and lipoproteins or in the uptake of radioactive iodine; it seems unlikely, therefore, that TSH has any action on the lipids and lipoproteins in the absence of functioning thyroid tissue.

The administration of l-thyroxine sodium 600 μg. daily for fourteen days to six hypercholesterolemic men with coronary disease resulted in significant depression of plasma total cholesterol and the C/P ratio (Table V). The lipoprotein ratio did not alter during the fourteen days therapy but there was a decrease in the concentration of cholesterol on the β lipoprotein fraction (Swahn, 1953).

Pituitary-Pancreatic Axis

Our investigations of the effect of growth hormone and glucagon on the circulating lipids and lipoproteins in the human are not yet definitive. In the rat, only growth hormone causes stimulation of hepatic cholesterol biosynthesis after it had been inhibited by hypophysectomy (Boyd and McGuire, 1955).

During the course of the administration of insulin 50 units daily to three men with depressive states there was no significant change in plasma total cholesterol, but the circulating phospholipids were elevated and the concentration of cholesterol on the β lipoprotein fraction was increased.

Discussion

Any theory of atherogenesis must explain the remarkable increase in the incidence of the clinical manifestations of coronary sclerosis. This increase might be attributed either to an increase in the factors suspected of contributing to the formation of atheroma and thrombosis, or to a decrease in the critical level at which the disease becomes manifest, or both; in either event, an equally fundamental change has occured in the natural history of the disease. An increase in the susceptibility of arterial and myocardial tissue to the factors responsible for atheroma and thrombosis might be analagous to changes which are thought to occur as a conditioning effect of stress (Selye and Heuser, 1954). Our environment is almost certainly stressful to some individuals, and it is surely significant that the remarkable social, economic and dietetic changes of this century have coincided with the evolution of clinical coronary disease.

It is considered that the circulating lipids and lipoproteins undergo physiological variation during the menstrual cycle and pregnancy as a result of endogenous hormonal influences, and it has been demonstrated that these lipids and lipoproteins can be influenced by the administration of certain hormones. At present their modes of action are obscure, but, as the level of circulating cholesterol is largely the net result of biosynthesis and catabolism of cholesterol in the liver, these hormones probably influence lipid metabolism through the liver. The maintenance of normal metabolism depends on an intact endocrine system, the secretions of which are continually adjusted to the requirements of the organism. Certain endocrine diseases result from hormonal insufficiency or excess and it is traditional to associate each of them with one particular disturbance of metabolism, such as the association of diabetes with a disturbance of carbohydrate metabolism; but carbohydrate, protein and lipid metabolism should really be regarded as a single integrated mechanism which is profoundly disturbed when its hormonal control is altered. Variations in the hormonal control of metabolism might result in changes in the circulating lipids and lipoproteins, and, without consideration of cause and effect, it is generally agreed that coronary sclerosis is associ-

ated with abnormal circulating lipids and lipoproteins; one asks, therefore, if it is also associated with hormonal imbalance. In fact, is coronary atherogenesis an endocrine problem? Is it possible that the changing environment of this century might be injurious to certain susceptible individuals who develop hormonal imbalance, and also develop decreased tissue resistance to the factors responsible for the production of atheroma and thrombosis? It is likely that investigation into these aspects of coronary atherogenesis will be rewarding.

In summary, then, many hormones influence the circulating lipids and lipoproteins. Ethinyl estradiol is effective in improving the abnormalities in the circulating lipids and lipoproteins which accompany clinical coronary disease. The question is raised whether coronary atherogenesis is partly an endocrine problem. It is thought that clarification of the complex interrelationships of the endocrine system may advance the understanding of the metabolic defects present in coronary sclerosis, and possibly lead to a therapeutic approach.

We wish to thank Dr. Rae Gilchrist and Professor G. F. Marrian, F.R.S., of our respective departments, for their advice and encouragement. The expenses for these researches have been defrayed by grants from the Secretary of State for Scotland and the Scottish Hospitals' Endowments' Research Trust through the Advisory Committee for Medical Research (Scotland).

References

1. Adlersberg, D.; Schaefer, L., and Drachman, S. R.: Development of hypercholesterolemia during cortisone and ACTH therapy. J. A. M. A., 144:909, 1950.
2. Antonini, F. M.; Piva, G.; Salvini, L., and Sordi, A.: Lipoproteine ed eparaina nel guardo umorale della chemiopatogenesi dell'aterosclerosi. Gior. geront., suppl. 1 (August) 1953.
3. Barr, D. P.; Russ, E. M., and Eder, H. A.: Protein-lipid relationships in human plasma. II. In atherosclerosis and related conditions. Am. J. Med., 11:480, 1951.
4. Boyd, G. S., and McGuire, W. B.: Hormonal influences in the control of plasma cholesterol and hepatic cholesterol synthesis in rodents. III Congrès International de Biochimie, Bruxelles, 1955.
5. Brown, J. B.: Urinary excretion of oestrogens during the menstrual cycle. Lancet, (1):320, 1955.
6. Conn, J. W.; Vogel, W. C.; Louis, L. H., and Fajans, S. S.: Serum cholesterol: a probable precursor of adrenal cortical hormones. J. Lab. & Clin. Med., 35:504, 1950.
7. Gertler, M. M.; Garn, S. M., and Lerman, J.: The interrelationships of serum cholesterol, cholesterol esters and phospholipids in health and coronary artery disease. Circulation, 2:205, 1950.
8. Jones, H. B.; Gofman, J. W.; Lindgren, F. T.; Lyon, T. P.; Graham, D. M.; Strisower, B., and Nichols, A. V.: Lipoproteins in atherosclerosis. Am. J. Med., 11:358, 1951.
9. Lober, P. H.: Pathogenesis of coronary sclerosis. Arch. Path., 55:357, 1953.
10. Mann, G. V., and White, H. S.: The influence of stress on plasma cholesterol levels. Metabolism, 2: 47, 1953.
11. Nikkilä, E.: Studies on the lipid-protein relationships in normal and pathological sera and the effect of heparin on serum lipoproteins. Scand. J. Clin. Lab. Invest., 5: suppl. 8, 1953.
12. Oliver, M. F., and Boyd, G. S.: Changes in the plasma lipids during the menstrual cycle. Clin. Sci., 12:217, 1953(a).
13. Oliver, M. F., and Boyd, G. S.: The plasma lipids in coronary artery disease. Brit. Heart J., 15:387, 1953(b).
14. Oliver, M. F., and Boyd, G. S.: The effect of estrogens on the plasma lipids in coronary artery disease. Am. Heart J., 47:348, 1954.
15. Oliver, M. F., and Boyd, G. S.: Plasma lipid and serum lipoprotein patterns during pregnancy and puerperium. Clin. Sci., 14:15, 1955(a).
16. Oliver, M. F., and Boyd, G. S.: Serum lipoprotein patterns in coronary sclerosis and associated conditions. Brit. Heart J., 17:299, 1955(b).
17. Oliver, M. F., and Boyd, G. S.: The effect of the sex hormones on the circulating lipids and lipoproteins in coronary sclerosis. Circulation (in press) 1956 (a).
18. Oliver, M. F., and Boyd, G. S.: Changes in the serum lipoproteins during the menstrual cycle. (To be published) 1956(b).
19. Rosenberg, I. N.; Young, E., and Proger, S.: Serum lipoproteins of normal and atherosclerotic persons studied by paper electrophoresis. Am. J. Med., 16: 818, 1954.
20. Russ, E. M.; Eder, H. A., and Barr, D. P.: Protein-lipid relationships in human plasma. I. In normal individuals. Am. J. Med., 11:468, 1951.
21. Russ, E. M.; Eder, H. A., and Barr, D. P.: Influences of gonadal hormones on protein-lipid relationships in human plasma. Am. J. Med., 19:4, 1955.
22. Selye, H., and Heuser, G.: Fourth Annual Report on Stress. Montreal: Acta, Inc., 1954.
23. Smith, G van S., and Smith, O. W.: The urinary excretion of estrogenic and gonadotropic hormones during menstrual cycles, the period of conception and early pregnancy. New England J. Med., 215: 908, 1936.
24. Steiner, A.; Kendall, F. E., and Mathers, A. A. L.: The abnormal serum lipid pattern in patients with coronary arteriosclerosis. Circulation, 5:605, 1952.
25. Swahn, B.: Studies on blood lipids. Scand. J. Clin. Lab. Invest., 5: suppl. 9, 1953.

Urinary Estrogen and Serum Protein-bound Iodine Levels

In a Group of Post-Menopausal Women With and Without Myocardial Infarction

JESSIE MARMORSTON, OLIVE HOFFMAN, HARRY SOBEL, and PAUL STARR
Los Angeles, California

IT is generally recognized that myocardial infarction occurs with considerably less frequency in cyclic women than it does in men of a comparable age group. Following the menopause, however, women become increasingly susceptible to this condition. Certain clinical and experimental evidence suggests that estrogen may be responsible for the "protection" of the premenopausal woman.[1,2,3] The postmenopausal woman continues to excrete a small quantity of estrogen in the urine which presumably arises from adrenal or residual ovarian activity. If estrogen is protective, it might be expected that postmenopausal women who have developed myocardial infarction excrete less estrogen than a comparable age group of female subjects who are free of this condition. An investigation was undertaken in order to determine if this is the case.

In the selection of cases, special emphasis was placed on subjects between the third and fifth postmenopausal years, although women within the ages of forty-seven to seventy-one were included. Individuals with diabetes, hepatic or renal diseases, as established by the usual laboratory procedures were excluded from this study as were those with clinical evidence of myxedema. Individuals with myocardial infarction were so classified only if there was unquestioned evidence of its occurrence by electrocardiographic and other clinical studies. The control group consisted of ambulatory patients without any evidence of cardiovascular disease as established by the usual clinical and laboratory criteria. In order to determine the effect of long-term debility, a "sick" control group was selected from hospitalized cases who had various long-term dyscrasias and were moderately to severely debilitated therefrom. These included lymphosarcoma, multiple sclerosis, severe secondary anemia, et cetera.

Urinary estrogen was determined biologically using the method of Migeon and Gardner with the exception that the extractions were made with ether.[4] The results were calculated for twenty-four-hour specimens and expressed as microgram equivalents of estradiol-17β.

Urinary estrogen was determined on the specimens from 23 postmenopausal women with myocardial infarction, nineteen "well" controls and eight "sick" controls. Fifty-five per cent of the women in the control groups excreted 0.50 micrograms of estradiol-17β equivalents or greater as compared to 22 per cent of the infarcted group. Preliminary study of the distributions of the estrogen values in the various groups showed them clearly to be skewed and that an exponential transformation normalized them with regularity. Statistical computations of these data were therefore made using the logarithms of the original values. Differences between the means of the well and sick controls were not significant so the two control groups were combined, giving a total of twenty-seven controls. The mean log value of this group was -.2886 (antilog .516 microgram equivalents of estradiol-17β. The mean log value for the myocardial infarct group was -.6127 (antilog .244 microgram equivalents of estradiol-17β). This difference was highly significant. ($p = < .01$).

As part of this investigation, the serum protein-

(Continued on Page 808)

From the Institute for Medical Research and the Department of Biochemistry, Division of Laboratories, Cedars of Lebanon Hospital and the Departments of Medicine and Biochemistry School of Medicine, University of Southern California.

Supported by a grant from the California Foundation for Medical Research.

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

The Coronaries

The Coronaries through the Ages

PAUL D. WHITE
Boston, Massachusetts

ALTHOUGH coronary heart disease has doubtless existed since the time of Adam, and may even have been responsible for his death, we have no recognition of it as a possible cause of morbidity or mortality until the year 1700. Inasmuch as current investigations strongly suggest that it is in large part a disease of civilized man, it may well have been rare in the stone age, when our ancestors dwelt in caves, and uncommon even in the Dark and Middle Ages. It has been an interesting though rather frustrating experience to try to trace its course from the earliest historical records to the present day.

The extraordinarily slow recognition of coronary heart disease through the ages is matched only by our ignorance of its etiology today, in September, 1955. It is fascinating to compare the current theories as to its causation. Some blame the stress and strain of modern life, others heavy labor and accidents, some tobacco, more still the various constituents of the diet, and some even today regard it fatalistically as God's will. A recent book has stressed the psychosomatic factors, opening with the admonition that "the fear of the Lord is the beginning of wisdom" and ending with the hope that "those who labor and are heavy laden" should seek spiritual aid for their health's sake. Probably we need both, a good psychosomatic attitude and good health habits. It may well be that, much as the padre in the Second World War is quoted as having said, "Praise the Lord *but* pass the ammunition," we should say, "Fear the Lord but do something else too in the way of preventive medicine."

Before Herrick

In the civilizations before Christ there is little or no note of illness or death that might now be interpreted as the result of coronary heart disease. Several Bible students have been unable to recall such instances and the historians of Egypt, Babylon, and Syria have not apparently uncovered reports of disease that might be interpreted as the result of defective coronary circulation. Prominent personages not infrequently died suddenly or after very short illnesses but almost invariably these deaths are to be ascribed to accidents, war, assassination, poisoning, and infections. It is possible once in a great while to blame the heart for certain troubles recounted by historians of ancient days but this is only by inference. To be sure, calcification has been noted in the arteries of Egyptian mummies but there is no record of such calcification of the coronary arteries so far as I know, quite possibly because of the lack of preservation of the hearts themselves.

There is perhaps a little circumstantial evidence in the history of Israel. For example, the High Priest Eli, as recorded in the first book of Samuel in the Old Testament, greatly disturbed by the news of the slaying of his sons and the seizure of the Ark of the Covenant by the Philistines, fell from his chair, perhaps as a result of a cardiovascular accident, and broke his neck. It is intimated that the fracture killed him rather than a heart attack, which may, however, have caused him to swoon. Incidentally it is of interest that his sons who were priests of poor repute had sinned against God in breaking the commandment not to eat fat and they were punished for that and doubtless other reasons too. They had partaken of morsels of fat from the sacrificial offerings. In the book of Leviticus, 7th Chapter, 22nd to 24th verses, the children of Israel had been ordered by Moses at God's command to avoid eating any fat from the ox, the sheep, or the goat. Whether

Presented in the Symposium on Arteriosclerosis, University of Minnesota, Minneapolis, September 7, 1955.

this was wholly a matter of sacrificial rite or whether it was already recognized as a measure of preventive medicine, like many other commandments, we have no way of knowing. It is quite possible that within a few years we may need to advise the American people to do with their diet what Moses advised the children of Israel to do some three thousand years ago.

Another reference in the first book of Samuel, Chapter 25, is of some interest. A prosperous land owner, named Nabal, obviously with considerable concern about his flocks and unsympathetic in his dealings with David, after a controversy with his wife and a feast at which he got quite intoxicated, suffered from an acute illness which prostrated him so that he lay like a stone for ten days before he died. He was, of course, "struck down by God"; but in all probability he suffered either from a cerebral vascular accident or a profound coronary heart attack, perhaps a punishment for his prosperity as in modern days. As one reads through the Books of Kings and the Chronicles in the Bible, looking for other possible examples of cardiovascular disease, one is struck by the numerous instances of assassination or death in war. When there is recorded what appears to have been natural deaths as in the case of David and Solomon, who ruled for forty years, it is said simply that they slept with their fathers.

So far as I am aware, we have no knowledge from records in the East in the writings of India and China of the existence of coronary heart disease. The average lifetime in Asia has always been short, being terminated early as a rule by accident, war, or infectious disease. However, three years ago I myself saw in consultation in New Delhi, India, a young native, twenty-nine years old, with typical myocardial infarction.

Historians of Greece and Rome have little more to add. Socrates died of hemlock poisoning. Alexander died at an early age of dysentery. Caesar was assassinated. In the Dark and Middle Ages, the duration of life was still grossly limited by wars, starvation, and pestilence. Although the coronary arteries themselves had been recognized by the Alexandrian anatomists, Erasistratus and Herophilus, and more fully described by Vesalius and Vieussens more than a thousand years later in the sixteenth century, disease thereof was not reported.

Unable myself to recall the names of prominent personages who may have suffered from coronary heart disease in ancient times in the Dark and Middle Ages, in the Renaissance, and in the writings of the great authors like Shakespeare, I have asked students of those eras and literary works to help me. Professor Gilmore, chairman of the Department of History at Harvard University, has written to me that he believes very few celebrated persons at the time of the Middle Ages and the Renaissance in Europe died from anything that could be diagnosed as heart disease. Also he stated that longevity was apparently quite rare; for example, Emperor Charles V considered that he was an old man when he resigned the crown at the age of fifty-five.

In more modern times coronary victims (probable or certain) include Matthew Arnold, Charles Dickens, Nathaniel Hawthorne, the Earl of Clarendon, Charles Bell, Sir James Mackenzie, Sir Thomas Lewis, Richard Cabot, President Harding, and Wendell Wilkie.

It was Bonetus who, in the second edition of his *Sepulcretum* published in 1700, reported the first association of a seriously pathological condition of the coronary vessels with rapid death. A fat poet, after a hearty meal and much orating, climbed a flight of stairs, was seized by great discomfort in his chest, and died within a few minutes. At autopsy he was found to have such narrowed coronary arteries that it was impossible even to insert the end of a needle into them. We do not know whether he had pain or not. The description was that of discomfort which might have been due to or associated with some difficulty in breathing.

In 1728, Lancisi wrote on Sudden Death, namely *De Subitaneis Mortibus*, in order clearly to demonstrate natural causes of sudden death. Although a number of interesting illustrations were given, including cerebral hemorrhage and aortic rupture, there was no clear instance of coronary occlusion. Nor did Senac or Morgagni do any better; the latter in 1760 did, however, wonder what symptoms might be produced by coronary narrowing. He thought that palpitation could perhaps be so induced. Eight years later in 1768 Heberden gave his classical lecture on angina pectoris which was not published until 1772, but he did not know or guess that

angina pectoris was due to coronary insufficiency. Within a few years, however, actually in the early 1770's, Jenner of smallpox fame noted calcification of the coronary arteries in the autopsy of a patient who died of angina pectoris. But since his close friend, John Hunter, had begun to have angina pectoris at about that time or shortly before, Jenner did not announce this discovery of his, confirmed by later autopsies, until 1799 when a famous letter of his was published in Parry's book entitled *Syncope Anginosa.* Parry cited several cases in that book. Fothergill (1776) and Black in 1794 published reports of cases of angina pectoris who showed postmortem ossified coronary arteries. Fothergill also described myocardial scars.

Thus, at the end of the eighteenth and the beginning of the nineteenth centuries, there was the clear recognition by a few individuals of this association of coronary artery sclerosis with morbidity and mortality. Despite this recognition a hundred and fifty years ago, the medical world was very slow in paying attention to its importance. A few scattered papers appeared here and there at the beginning of the century, such as that by John Warren on page 1 of Number 1 of Volume 1 of the *New England Journal of Medicine,* published in Boston in 1812.

When the *New England Journal of Medicine* changed its name to the *Boston Medical and Surgical Journal* in the late 1820's, it was the custom to record the deaths in Boston week by week. I have selected the year 1829 to peruse the causes of death of Bostonians and have found the following. Among the total deaths of 1,221, the most common cause was consumption, that is, tuberculosis, with 203 cases. Many other infections played their role also. Pneumonia was second with ninety deaths and measles third with seventy-two. In searching for cardiovascular deaths, I discovered that "old age" was cited sixty-five times; it is almost certain that a good many of that group died from diseases of the heart and arteries. Apoplexy was specifically mentioned twelve times in addition and twelve others had dropsy. Interestingly enough, the diagnosis in only seven individuals was noted as that of "sudden death." Rare cases died of "enlargement of the heart," of "disease of the heart," of "palpitation of the heart," of "complaint of the heart," and of "ossification of the heart." Rheumatic fever was recorded in very few individuals as a cause of death. Although angina pectoris had been described and clearly recognized during several earlier decades, and although it was the title of the very first paper published in the *New England Journal of Medicine,* there was not a single diagnosis of angina pectoris as a cause of death in Boston in that year 1829. There were 160 persons who died of "diseases unknown"—this miscellany may well have included some "cardiacs" and coronary cases as well as diabetics, who were not noted at all in the table, and individuals who had obscure cancer or blood diseases.

It has been of further interest to determine the average ages at death of the male and female Bostonians in the year 1829. Almost exactly half of 1,221 persons who died that year were tabulated by sex and age. There were 303 males and 305 females, a total of 608. The males averaged only 23.5 years at death, the females 26.8 years, and both sexes together 25.2 years. This is in contrast to Bostonian males and females in 1953 who averaged 67 and 72 years respectively with total average of 69.5 years. In the year 1829, one quarter of the deaths (154 or 25.3 per cent) occurred in infants aged two years or younger, and only forty-six (7.6 per cent) lived to the age of 70 years or more. In 1953, only 4.7 per cent died under the age of five years, while 45 per cent died at 70 and over. The death rate in Boston in 1829 was 1,221 out of 61,392 inhabitants, which was almost exactly 2 per cent. The Boston death rate in 1953 was 1.2 per cent. From all these figures, it is quite evident that one important reason why there was undoubtedly less coronary heart disease in 1829 in Boston than now was the fact that the average Bostonian lived too short a life to acquire it. Other important reasons were, of course, failure to look for it and inadequate techniques. Just how great an increase there actually has been no one knows.

Medical writers continued to pay scant attention to coronary heart disease in the middle of the century and even towards the end of it. Austin Flint stated in his writings in the 1870's that he had rarely seen angina pectoris in his practice in New York City; he said, in

fact, that an interval of five years had passed without his having had such a patient, a statement which has seemed incredible. This observation of his meant that he was either not recognizing cases of the sort, at least the milder ones, perhaps on the basis of inadequate history taking, or that the disease was actually rare in one of the large cities in this country. Quite possibly both factors are to be given equal credit. On the other hand, pathologists were quite aware of coronary sclerosis during the last few decades of the century; among them were Weigert in 1880, Cohnheim in 1881, Ziegler in 1881, Huber in 1882, and Leiden in 1884. Marie in 1896 published a thesis on myocardial infarction. A few internists, in particular Osler in 1910 did lecture on angina pectoris.

This brings us well into the twentieth century. My own teachers at the Harvard Medical School, almost all of whom were in active practice, were cognizant of angina pectoris and its serious significance, but hardly mentioned it in their teachings, absorbed as they were by infectious diseases. These teachers of mine included Frederick Shattuck, Henry Jackson, Henry Christian, and Richard Cabot. Later when I was an intern at the Massachusetts General Hospital, my attention was rarely called to this disease. We were still swamped with the problems of infection which included in particular dysentery, typhoid, syphilis, the so-called contagious diseases, and tuberculosis. The age range of the patients in the medical wards was far lower than it is today. There was no room for middle-aged or older patients with which we are now overburdened, patients with cancer, arthritis, and cardiovascular diseases.

While I was an intern in the hospital in 1912, James Herrick of Chicago established his immortality in medical history by his recognition and description of the clinical entity of coronary thrombosis, but, strange to say, although he presented his paper before learned colleagues at a national society meeting, little or no attention was paid to it for the next ten years. This was doubtless in part due to the First World War, but whatever the cause, it is another example of the slowness with which important scientific contributions were recognized in former days.

My own early experience at the Massachusetts General Hospital for the ten years from 1912 to 1922 was interwoven with a year of study under Thomas Lewis in London in 1914, a few months in the British Expeditionary Forces back of the Somme in 1916, a year and a half in a General Hospital in the A.E.F. in France from 1917 to 1919, and six months on a relief mission to Greece in Macedonia in 1919. In none of these experiences or in the clinics at the Massachusetts General Hospital was I more than faintly aware of the existence of angina pectoris and certainly I did not recognize coronary thrombosis. I recall that in 1920 I was asked to see in consultation a prominent surgeon from another state who was visiting a New England colleague at his summer place. This surgeon had been afflicted by what he thought himself, and to which his medical and surgical friends agreed, was an attack of cholecystitis complicated by pericarditis. I was asked to bring along a needle and syringe for a pericardial tap but I found this unnecessary since the pericarditis was quite dry. There was a very slow recovery from this illness, and shortly after his return home to Cincinnati there was evidence of heart involvement. An electrocardiogram was taken and sent to us. As I recall it now, there was a marked abnormality of the T waves which we noted but did not recognize as pathognomonic of any particular condition. Shortly after this, however, that is, by 1921, most of us had begun to be aware of the clinical condition of coronary thrombosis and its electrocardiographic manifestations.

There were a few exceptional individuals who recognized the disease earlier, two of whom were Samuel Levine of Boston, who in 1918 wrote an article entitled "Infarction of the Heart Simulating Acute Surgical Abdominal Conditions," and L. Whittington Gorham of Albany, who in 1920 published a paper entitled "The Significance of Transient Localized Pericardial Friction in Coronary Thrombosis (Pericarditis Epistenocardica)." Levine has told me that at the time he prepared his paper he was unaware of Herrick's important contribution of six years earlier. Incidentally, Levine published an important monograph on coronary thrombosis in 1929.

My Own Generation

Thus, the present generation has slowly and painfully acquired knowledge about the coronary

circulation and its diseases, which, of course, are almost wholly summed up in the one word "atherosclerosis." I would like to interpolate at this point a brief observation, namely that we as internists have been even slower in the recognition of the importance of cerebral atherosclerosis. We have left this problem largely to be dealt with by our neurological colleagues, but we should certainly share the responsibility with them.

My own private practice started in 1920, and I have recorded the diagnoses of all my private patients from the beginning — etiologically, structurally, and functionally. During the first year of my practice in 1920 I did not make a single diagnosis of coronary thrombosis. The first case clearly so recorded was that of a man aged seventy-one, whom I saw in consultation with my father on January 13, 1921. He died thirteen days later in pulmonary edema. During the years 1921 and 1922 I made the definite diagnosis of coronary thrombosis in nine cases and questionably in five more. Meanwhile a diagnosis of "cardiosclerosis" or of "arteriosclerotic heart disease" with or without angina pectoris was not at all rare. The most common occurrence of so-called arteriosclerotic heart disease or cardiosclerosis (these terms were used interchangeably) was in the case of older individuals, that is, those more than fifty years old who had any arrhythmia or cardiac enlargement. Such was the custom in diagnosis that we now have happily long outgrown since we know that arrhythmias can occur at any age without any underlying structural heart disease and that hypertension is a common cause of cardiac enlargement.

To continue with my own personal experience, I have looked up the cases which I diagnosed definitely as coronary thrombosis in the years 1925, 1935, and 1945. During those years my practice remained much the same in character, consisting almost entirely of patients with cardiovascular signs or symptoms. During the earlier ten years of my practice I was seeing more patients annually than later but the percentages are of interest and importance.

In 1925 out of 501 new cases in my own practice, I diagnosed coronary thrombosis definitely thirty-two times, in twenty-five males and seven females. This is 6 per cent. I would add that there was one male under the age of forty and that two of the females had diabetes. During that same year there were six questionable male cases and two questionable female cases.

In 1935 out of 357 new cases of my own, I saw a total of forty-eight patients in whom I diagnosed definitely coronary thrombosis; forty-five of these were male and three were female. There was one male under forty. Thus, during that year the percentage of coronary cases in my practice increased to 13 per cent. In 1935 there were in addition six questionable male and four questionable female cases of coronary thrombosis.

In 1945, out of 351 new cases seen in private practice, there were seventy-one cases definitely diagnosed by myself as coronary thrombosis, which gives a percentage of 20; fifty-seven of these cases were male and fourteen female. There were three males under the age of forty, and two of the females had had myxedema. During that same year there were thirteen males questionably affected by coronary thrombosis, two of whom were under forty, and there were three questionable females. Thus, there was a steady rise in those three years at decade intervals from 6 per cent to 20 per cent.

I hasten to add that I am not including in this category all the cases of coronary heart disease, inasmuch as there were a good many patients with definite angina pectoris without myocardial infarction, actually more than I was seeing with coronary thrombosis and myocardial infarction. Nor have I included the relatively few cases of the Adams-Stokes syndrome.

I would like at this point to acknowledge my indebtedness, and that of some of my cardiological colleagues in Boston, to Timothy Leary who demonstrated to us in those early years the microscopic pictures of coronary artery atherosclerotic lesions and occlusion and myocardial scars too. During those early days it was not always the rule for pathologists in medical schools or hospitals to examine the coronary arteries in great detail. Also not infrequently, as I myself discovered, small myocardial infarcts, both old and new, were being overlooked. I remember one case with a small posterior myocardial scar visible under the posterior cusp of the mitral valve, once the chordae tendinae had been cut, and with a very small patch of adherent pericardium posteriorly, which had been overlooked by the pathologist but which clin-

ically we had diagnosed. Thus it is that some of the increased frequency of coronary heart disease is more apparent than real but how much no one knows. Some authorities have, however, stated that, on searching back in old hearts preserved from former years in pathological museums and pathological protocols, coronary heart disease was not uncommon and that there has not been so great an increase in its frequency noted by pathologists as by practicing physicians, but it hardly seems possible from our general clinical experience that coronary heart disease even at the same ages was as common a generation ago as it is now.

There is one other important contribution that I would like to pay tribute to at this time and that is the fundamental work by Schlessinger and Blumgart concerning the ramifications of the coronary circulation, both normal and abnormal. They demonstrated clearly the relationship of the site of the coronary thrombosis to the location of the resulting myocardial infarction and most important of all they made the discovery of the vital importance of the development of a collateral coronary circulation in the restoration of improved myocardial oxygenation and restoration of health, often with complete clinical recovery.

I would like now to end this part of my story with a few of the more important conclusions concerning the clinical aspects of coronary heart disease resulting from this experience of my own. I feel quite sure that many of my colleagues who also have been in clinical practice for a good many years will have had the same experience.

1. It is very important to recognize the degree of trouble. One may have the least possible amount of coronary heart disease to diagnose or one may have it so severely that death comes at once from coronary insufficiency or within a few hours from a fulminating attack of myocardial infarction. In between these two extremes there are all grades and manifestations of the disease. There is no strictly average case, although there are a good many who are close to the middle line. I often tell my patients who have a slight degree of angina pectoris on effort that they are very little different from their colleagues and friends of the same age who are free of symptoms. Doubtless some of these individuals who seem to be free of symptoms could have angina pectoris or even die if they should run very hard for a train or engage in very unusual strenuous exercise carrying as they do a considerable amount of so-called silent coronary atherosclerosis. Thus there may be only a few per cent difference between the middle-aged man who has angina pectoris and the middle-aged man who hasn't. In summary, one may have, just as in the case of many other conditions, such as respiratory infections or accidents, a touch of trouble or a fatal amount.

2. In addition to the variation of the degree of trouble there is often a considerable variation in the symptomatology thereof. Some individuals are hypersensitive and are aware of very little actual disease. Others are so insensitive that they may be almost mortally ill before they are aware of it. In my own experience with patients I have found that the heavy use of alcohol tends to favor the suppression of symptoms which may be important. One must, therefore, judge the person himself as well as the disease in diagnosis, prognosis, and treatment.

It is quite probable that a failure to take into consideration the two points I have just mentioned may account for at least some of the apparent increase of coronary heart disease as diagnosed today in comparison with that of twenty-five to fifty years ago.

3. There has been often a good deal of difficulty about nomenclature and a variety of terms have come into usage which are sometimes confusing. I myself was guilty of some of that years ago when I separated off in the first two editions of my book angina pectoris as a functional entity from coronary heart disease. It is true that there are a few cases of angina pectoris due to coronary insufficiency without any coronary artery disease but they are uncommon. Such cases include patients with syphilitic aortitis causing coronary mouth narrowing, or severe valvular stenosis, either aortic or mitral, with inadequate cardiac output and, therefore, inadequate coronary blood supply, and a few other causes, not commonly operating in the same way, however.

To my mind it is simplest to speak of coronary heart disease as an abbreviation of coronary atherosclerotic heart disease with its various subdivisions as shown by simple coronary in-

sufficiency (usually angina pectoris) on effort, coronary thrombosis with or without infarction, and heart block, bundle branch or a-v, with or without the Adams-Stokes syndrome.

4. At the same time that during the last generation a correction has been made in changing the diagnosis of acute indigestion in many patients to coronary heart disease, especially to acute coronary thrombosis, and adding cases to the coronary category who had been underdiagnosed because of the mildness of their attack or of their long survival, or because of lack of electrocardiographic evidence, there has developed an opposite tendency to overdiagnose coronary heart disease in some cases in whom indigestion, in particular cardiospasm, really does exist as a cause of symptoms, or in whom pericarditis may be confused with acute myocardial infarction. Happily the old custom still too prevalent in a good many places of labeling any older patient with arrhythmia or cardiac enlargement as having "arteriosclerotic heart disease" or "cardiosclerosis" is on its way out. Many persons seventy or eighty years old who may have premature beats or paroxysmal tachycardia or atrial fibrillation have no important heart disease, coronary or otherwise, and some of them have had arrhythmias of the sort ever since they were twenty years old. Also a good many of the persons who have enlargement of the heart of unknown cause or due to unrecognized hypertension in the past or present have been wrongly labeled arteriosclerotic heart cases.

5. One of the most dramatic changes that has come in our understanding of coronary heart disease during the last generation is that which concerns prognosis. It was customary in the early 1920's to regard the fate of individuals with either angina pectoris or coronary thrombosis, but more particularly the latter, as very dark. It was generally believed by the medical profession as well as by the laity that life would extend for only a few years at best and that it was likely to be quite an invalid life at the same time. Hence, I well remember hearing many persons say that since their life would be a short one, it might as well be a merry one, and all caution was thrown to the winds. A strenuous and gay life was carried on, and this, to be sure, did not infrequently end abruptly in a relatively short time. Their motto was: a short life, therefore a gay one. As time passed, however, many patients clearly diagnosed as having angina pectoris or coronary thrombosis, or both, were found not only to live along year after year but actually to recover fair health if not indeed in some cases good or excellent health. Many patients got perfectly well again and have continued so for many years.

One of the cases that I saw myself in consultation during a rather severe attack of acute coronary thrombosis in 1927 when he was fifty-one years old is perfectly well today after twenty-eight years. Now, seventy-nine years old, he is able to play golf without symptoms and yet with a moderately large scar in his heart.

It is quite obvious now that one of the reasons why coronary heart disease was underdiagnosed in the 1920's and possibly in the 1930's too was that if there was recovery it was commonly said that if the patient recovered or lived more than a few years, the original diagnosis must have been wrong. At the present time, the average duration of life after the first symptom of coronary heart disease is somewhat more than ten years and this includes those who die quickly as well as those who survive twenty-five years or better. This change in viewpoint naturally affected greatly our attitude toward the disease and has influenced our opinions about treatment.

6. Thus, following up what I have just said, the prognosis and treatment of coronary heart disease must be very carefully individualized. Although there are a few simple general rules, no two patients are exactly alike and therefor the therapy must be made to fit the individual case. Most often no very special treatment at all is necessary except for a full discussion with the patient of what we know and what we don't know about the disease and the application of common sense measures. Very few medicines are important, although specifically we do use a good deal of nitrite therapy in a prophylactic way as well as in the treatment of the symptom of angina pectoris. We employ rest and often anticoagulants at the time of an attack of coronary thrombosis with myocardial infarction and we do prescribe a low calorie and especially a low fat diet for individuals who are either candidates for coronary heart disease or who have had evidence thereof, especially if they are overweight and their serum

cholesterol content is high. More important, however, than all such therapy is our current intensive study of coronary heart disease with a view to prevention.

The Future

It is quite obvious from what I have already said and from the extensive program of the present symposium that coronary heart disease is tremendously in the limelight in this country today. It is also quite obvious that research with a view to its prevention is of prime importance. The laboratory study of animals, the clinical study of patients, and, of at least equal importance, the epidemiological studies throughout the world, well conducted by international teams, must receive full support. It should be possible within the next decade to learn so much from all these researches that we can give useful advice to the candidates for early coronary heart disease to prolong their lives and years of usefulness and happiness. Not only does this apply to the citizens of this country but to the people in every nation in the world who are inclined, as a result of their increasing prosperity, to live the way most Americans live today.

RESEARCH IN ARTERIOSCLEROSIS

(Continued from Page 745)

one-sided and uninhibited claims of success. Physicians and scientists must preserve their heritage of criticism. Without it they will not build a tower of knowledge for too many unsound struts will have been introduced to support it.

So whether we think arteriosclerosis is due to smoking, drinking, eating too much of everything or just too much fat, too much or too little exercise, too much or too little vitamins, too much or too little protein, too much or too little thyroid, let us remember that there are differences among people and among peoples. There are those who might care to become Bantus, there are those who might care to go back to Methuselah and I only hope that there are few of us who, for the sake of a placque in our arteries, would care to abolish those small or large differences which make us men and women. Investigators must find a better solution to the problem than that.

URINARY ESTROGEN AND SERUM PROTEIN-BOUND IODINE LEVELS

(Continued from Page 800)

bound iodine was determined in thirty-eight postmenopausal women with myocardial infarction and forty-seven control subjects. A modified Barker procedure was used.[5] Forty-two per cent of the patients with myocardial infarction had PBI values below 4.6 micrograms per 100 cc. of serum, whereas only 11 per cent of the control group were in this category. The mean PBI value for the former was 5.10; the latter 5.81. A statistically significant difference was found. ($p = .05$).

These observations suggest that diminished estrogen and thyroxine production may play an important role in the occurrence of myocardial infarction in postmenopausal women.

Acknowledgment

The authors wish to thank Dr. Frederick J. Moore for the statistical analyses of the experimental data and Mr. George McGee for his invaluable technical assistance.

References

1. Barr, D. P.: J. Chronic Dis., 1:63, 1955.
2. Pick, R.; Stamler, J.; Rodbard, S., and Katz, L. N.: Circulation, 6:858, 1952.
3. Eilert, M. L.: Metabolism, 2:137, 1953.
4. Migeon, C. J., and Gardner, L. I.: J. Clin. Endocrinol., 12:1513, 1952.
5. Barker, S. B.: J. Clin. Investigation, 30:55, 1951.

Case Presentation

DIABETES INSIPIDUS AND PREGNANCY

CHARLES H. McKENZIE, M.D.,
and FRANCIS M. SWAIN, M.D.
Minneapolis, Minnesota

THE coexistence of diabetes insipidus and pregnancy is a rather infrequent condition. This is attested by the fact that Williams stated that the incidence was nineteen cases per 100,000 admissions.

According to Lake,[1] Frank in 1794 was the first person to describe adequately a case of diabetes insipidus. Before this it had been confused with diabetes mellitus. Lake[1] also states that Von Velden and Farini independently commented on the efficacy of pituitary extract in controlling the polydipsia and polyuria. Diabetes insipidus is apparently due to a deficiency of an antidiuretic factor normally produced in the posterior lobe of the pituitary gland. According to Ranson and associates (quoted by Carfagno et al[2]), there are nuclei located in the hypothalamus which control the functions of the posterior lobe of the hypophysis. About 63 per cent of diabetes insipidus cases are due to tumor, 10 per cent to trauma, and the rest due to infections (lues, encephalitis) and idiopathic.[1] The dominant symptoms and signs are of polydipsia, polyuria, and urine of consistently low specific gravity. According to Von Hann (quoted by Carfagno et al[2]) and Richter,[3] the anterior lobe of the pituitary must be intact in order for diabetes insipidus to develop. Patients with Simmonds' or Sheehan's disease do not have diabetes insipidus. Carfagno and colleagues[2] believe that the anterior lobe of the hypophysis exerts its diuretic effect through the adrenal cortex, and that this effect is delicately balanced by the antidiuretic effect of the posterior lobe. They also feel that the thyrotropic hormone of the anterior lobe may play a part, and that the placenta itself may secrete a diuretic factor. Therefore, quoting Carfagno again, there are several factors which increase the diuretic effect in pregnancy itself: The stimulation of the adrenal cortex, the stimulation of the thyroid, the placental factor, and the diuretic effect of increased nitrogenous wastes of pregnancy.

Soule[4] in 1937 found thirty-six cases of diabetes insipidus associated with pregnancy and added one of his own. At that time he made some observations on the previous cases: (1) The consistent lack of demonstrable posterior pituitary lesions (as determined by skull x-rays), (2) the infrequent accompaniment of a positive Wassermann reaction, (3) the frequent occurrence of premature labor, and (4) the uniform response to posterior pituitary extract.

It seems that the most consistent finding in diabetes insipidus with pregnancy is the remarkable variety. The disease may be aggravated by pregnancy, or may be unaffected or even ameliorated during pregnancy. Diabetes insipidus may be transitory during pregnancy, may have its onset during pregnancy and persist afterwards, or may appear transiently following delivery. Novak (quoted by Blotner and Kunkel[5]) reported a patient in whom diabetes insipidus developed during her first pregnancy and disappeared post-partum, the same sequence of events recurring in her ten subsequent pregnancies. Weil (also quoted by Blotner and Kunkel[5]) and his son studied five generations of a family of 220 members, headed by a man with diabetes insipidus, of whom thirty-five developed the disease.

Case Report

The patient was eighteen years old when first seen in 1949. She was followed through a normal pregnancy which terminated in a normal delivery under saddle block anesthesia in that same year. Her post-partum course was uneventful. In February, 1951, she had German measles (rubella). Following this she developed intense headache and general malaise. In retrospect, it is possible this may have represented a post-rubella encephalitis. In the early part of July, 1951, she developed polydipsia, polyuria, anorexia, ataxia, dizziness, etc. She was seen by an internist who found a twenty-four-hour urine output of 10,100 cc., with a specific gravity of from 1.001 to 1.005. She was given

From the Asbury Methodist and Abbott Hospitals, Minneapolis, Minnesota.

This report was presented at Medical Grand Rounds of Asbury Methodist Hospital, Minneapolis, Minnesota, May 5, 1955.

TABLE I. RESUME OF TWELVE RECENT CASES OF DIABETES INSIPIDUS AND PREGNANCY

Author and Year	Etiology	Unusual Symptoms	Treatment	Course of Pregnancy	Type Labor	Baby	Later Course
Greene and Gibson (1938)[7]	?	Diabetes mellitus, infrequent menses	Nasal insufflation of pituitary	Normal pregnancy diabetes insipidus better	Normal	Died on second day of brain injury	Intranasal pituitary continued post-partum
Carter (1940)[8]	?	Sterility 5 years Scanty menses, poorly developed secondary sex characteristics	Procedures for sterility ineffective till pituitrin used	Continued with pituitrin till 7½ months	Normal except for cephalopelvic disproportion and head did not engage	Stillborn by Cesarian section 9 lbs.	No pituitrin after pregnancy, had output of 4-5 liters
McLaren and McLeod (1942)[9]	Fell in 22nd week of pregnancy. Hit side of head x-ray ok. Traumatic?	None	No pituitary extract. Disease began in pregnancy and ended post-partum	Diabetes insipidus developed at 34 weeks. Abruptio and hepatitis at 36 weeks	Induced by amnionotomy. Normal contractions	Died during labor 6 lbs. 2 oz.	Pitressin daily post-partum. Hemorrhage on third day. No recurrence of diabetes insipidus
Blotner and Kunkel (1942)[5] 2 cases	? Had it for 9 years before pregnancy	Dysmenorrhea caused by the pituitrin injections	Used pituitary insufflation throughout pregnancy	Disease worse Output increased up to 7 months then decreased till term	Normal	Normal 8¼ lbs.	Output continued at 8 liters. Pituitrin was continued afterwards
	Had it during a previous pregnancy	None	None	Diabetes insipidus reappeared in fifth month of present pregnancy. Became worse	Repeat Cesarian section done 18 days before term	Twins normal	Symptoms disappeared post-partum and were absent for at least 3 months
Maranon (1947)[10] 1 patient with diabetes insipidus in 3 pregnancies	?	None	Treated for 12 years before pregnancy. Continued treatment during pregnancy with pituitrin	Diabetes insipidus unchanged during pregnancy.	Labor began, then stopped	Stillborn	See next pregnancy
	Had 3 month abortion						
			Treated with pituitrin	Went to term	Inertia was treated with pituitrin. Normal delivery	Normal	See next pregnancy
			Same treatment	Went to term	Inertia. No pituitrin, 3 day labor	Stillborn	At 43 years of age still had 11 liters urine output
Lake (1947)[1]	Fever at 17 years age. Encephalitis?	Weakness weight gain scanty menses absence of libido—hirsutism	Pitressin tannate	Had diabetes insipidus in a previous pregnancy, continued in this one	Inertia. Forceps	Normal	Disappeared post-partum. Became pregnant third time Diabetes insipidus recurred and she was aborted
Tannenbaum, Bertling, and Burwell (1952)[11]	?	None	Pitressin tannate	Needed less pitressin as pregnancy went on. None after 6 months	Normal—low forceps	Normal, average size	48 hours after delivery resumed pitressin
Carfagno, Durant, Shuman (1953)[2]	?	None	Developed diabetes insipidus in a previous pregnancy, continued pitressin in this one	Used pitressin till onset of labor	Normal. No pituitrin. Spontaneous delivery	Normal 7 lbs.	Diabetes insipidus disappeared post-partum
Hickey, Keette (1954)[12]	?	None	Pitressin before pregnancy continued	Pitressin used all through pregnancy till 24 hours before induction	Normal Spontaneous delivery	Normal	No mention
McKenzie, Swain (present report)	Post-rubella encephalitis	Irregular menses Sterility till diabetes insipidus under control	Pitressin tannate before and during pregnancy	Required less pitressin as pregnancy progressed. None at all last 10 weeks	Normal	Normal 6 lbs. 14¾ oz.	No return of diabetes insipidus post-partum

pitressin in the office but she developed carpopedal spasm and generalized cramps and was hospitalized. General physical and neurological examinations were essentially negative. An x-ray of the skull showed the sella turcica to be normal. The Wassermann reaction was negative, the blood urea nitrogen 7 milligrams per cent, the blood sugar 83.5 milligrams per cent. She was placed on pitressin tannate in oil 1 cc., intramuscularly twice daily. With the pitressin injections, both intake, output, and specific gravity became normal. She was sent home after two weeks in good condition. She continued on the medication twice a day for a while, then once a day in late 1951. In 1952 it was used once every other day, and in 1953 once a week and finally, once a month. During the first part of 1954 it was also necessary once a month. The patient's menses were grossly irregular from the time of the rubella (February, 1951) till April or May of 1954.

Her last menses occurred on June 8, 1954. She continued taking pitressin during the first part of her pregnancy. For a while she required injections oftener, from two to seven times monthly depending on symptoms. The need for them gradually decreased so that during the last ten weeks she needed none at all. The membranes ruptured spontaneously at term on March 14, 1955, and labor began three and one-half hours later. The first stage lasted eight hours, the second was terminated by low forceps after fifteen minutes, and the placenta was delivered five minutes later. The uterine contractions were normal throughout. The patient received no pitocin or pituitrin but did get the routine ergotrate on delivery of the head. The blood loss was estimated at 50 cc. The baby was quite normal and weighed 6 pounds 14¾ ounces. There was no return of the polydipsia or polyuria during the hospital stay, and the specific gravity of the urine during this period ranged from 1.009 to 1.032. When the patient returned for her six-week post-partum examination on April 22, 1955, she stated she still had no return of symptoms. Pelvic examination was entirely normal. She had not had any pitressin since December, 1954.

Since Soule's report (1937) of the thirty-seven cases of diabetes insipidus in pregnancy, we have been able to find eleven additional cases reported. The case herewith reported makes a total of forty-nine.

Discussion

In this portion we shall be concerned with the eleven recent cases of diabetes insipidus and pregnancy we have culled from the literature, and our own case.

Of these twelve, only one could possibly have developed diabetes insipidus as a result of trauma and this is doubtful. There were two patients in whom the disease may have occurred as a result of encephalitis. There were none in whom tumor or lues could be proved as a cause. Four of the patients had irregular or scanty menses; this was accompanied by decreased fertility in two of the four.

In ten of these twelve patients the disease began before pregnancy, the remaining two had the onset of diabetes insipidus during pregnancy. In four of the patients the disease was less severe or disappeared during pregnancy, in three it became worse and in the remaining five it was unchanged. The disease disappeared after pregnancy in five patients, persisted in six, and in the other there was no mention of the post-partum course. We concur that the outstanding feature of diabetes insipidus in connection with pregnancy is its great variety!

Two of Soule's observations can be borne out by our review: There was no x-ray evidence of a pituitary lesion in any of the patients, and there was no relationship between the disease and syphilis. His other two observations are more controversial. He felt that premature labors were more common; this may have been the result of using pituitrin injections or nasal insufflations of pituitary extract instead of pitressin injections. The only premature labor in this series was induced by amnionotomy because of abruptio placenta, and this patient received no pituitary preparations prior to this procedure. Soule also stated that there was uniform good response to posterior pituitary therapy. In one of the present group the author stated that pitressin failed to control the polyuria. In two others the disease was described as becoming worse despite treatment.

Treatment of these patients was divided between pituitary nasal insufflations, pituitrin and pitressin injections. In some, whole posterior pituitary, whether given intranasally or by injection, seemed to cause annoying uterine contractions whereas the pitressin did not. Two of the patients developed uterine inertia during labor, one of these had inertia in three successive pregnancies. However, in the light of the work of Fisher et al[6] one might expect a higher incidence of inertia. These authors were able to demonstrate the occurrence of uterine inertia in cats and monkeys when the stalk of the hypophysis was cut.

Summary and Conclusions

1. The theory of the pathologic physiology of diabetes insipidus has been briefly reviewed as have the various etiologies.

2. The incidence and significance of its coincidence with pregnancy have been discussed.

3. Eleven recent cases of coexistent diabetes insipidus and pregnancy are reviewed and one of our own has been reported.

(Continued on Page 813)

Laboratory Aids

Sponsored by
The Minnesota Society
of Clinical Pathologists
George G. Stilwell, Editor

EXFOLIATIVE CYTOLOGY: A REALISTIC APPRAISAL

JOHN R. McDONALD, M.D.
Rochester, Minnesota

It is now almost thirty years since the cytologic examination of exfoliated cells was developed as a diagnostic test for cancer. As with many new methods, immediate acceptance of the technique was not widespread. During the past ten years, the method has been tried with regard to every conceivable bodily orifice and secretion, with different degrees of success. The reaction to this technique has varied not only among individuals but among groups of specialists. Some groups have been most enthusiastic, whereas others have been frankly skeptical. For example, many gynecologists have accepted the method as one that eventually may eliminate carcinoma of the cervix as a cause of death. Gynecologists are of the opinion that cytologic study of cervical smears should be done at regular intervals (six months to one year) on all women more than thirty years of age on the assumption that this procedure would lead to the recognition of carcinoma of the cervix in its preinvasive stage and that the treatment of this lesion would eliminate subsequent infiltrative carcinoma of the cervix. So enthusiastic have some gynecologists become that a number of them make pathologic studies of and interpret cervical smears and even smears from other material. A national organization for exfoliative cytology has been formed largely through the efforts of certain gynecologists.

By contrast, pathologists have been skeptical toward exfoliative cytology. Their reasons have been valid in most instances. Pathologists maintain an inborn cautiousness toward the acceptance of an untried technique. Furthermore, the successful performance of this technique can be accomplished only by the generous use of the pathologist's time, a scarce commodity; thus, many pathologists have concluded that the procedure is neither economical nor practical. Also, many pathologists have feared that positive reports as the result of studies on such smears would be accepted by clinicians as proof of the presence of carcinoma, with no further efforts being made to perform biopsy. This, of course, could lead to unfortunate treatment.

The mails recently have been flooded with literature concerning the Cancer Cytology Foundation of America, Inc., whose president is Dr. J. Ernest Ayre. This is an organization to provide a mail-order service in cytology on a nationwide basis. It does not appear that this approach to the practical application of exfoliative cytology is the one that is best fitted for the sound practice of medicine.

The greatest field for usefulness of exfoliative cytology apparently lies in the field of cervical cytology. As this test is now done, the cells that are examined are not exfoliated but are living cells scraped from the cervix; hence, the term "exfoliative" is not strictly accurate. The cervical smear is at its best in the diagnosis of carcinoma *in situ* of the cervix. Fairly good evidence exists that at times certain instances of cervical carcinoma *in situ* later have become infiltrative. However, considerable disagreement is present among pathologists as to what constitutes cervical carcinoma *in situ*. Siegler[1] sent to twenty-five pathologists a group of twenty slides that represented difficult and borderline problems in the histologic diagnosis of cervical carcinoma *in situ*. Complete diagnostic agreement was not obtained on any of these slides. Every individual slide was believed to represent a malignant lesion by at least one observer.

Less useful fields for exfoliative cytology include the lung and pleural and peritoneal fluids. However, carcinoma of the lung only occasionally is diagnosed solely on the basis of cytologic ex-

From the Section of Surgical Pathology, Mayo Clinic, Rochester, Minnesota.

amination. Evidence of a pulmonary lesion in the lung usually is present in thoracic roentgenograms, a fact that, by itself, renders an operation imperative; also, "positive" results of bronchoscopic biopsy are more accurate than are "positive" results of cytologic studies. "Positive" results of the cytologic examination of ascitic fluid are falsely positive in at least 5 per cent of cases, so this technique is not completely reliable. It is highly questionable whether much value can be attached to routine cytologic examination of lesions of the skin, oral cavity, rectum or breast. Examination of gastric material, regardless of whether or not the Ayre "rotating gastric brush" or similar instruments are used, is of questionable practical value.

It is commendable that the American Board of Pathology has included exfoliative cytology in its examinations. The American Society of Clinical Pathologists has included this topic in one of its annual workshops. It appears that pathologists should take a more active interest in cytology to see that these techniques are done properly and ethically. In this regard, the pathologist is best suited for the performance of the test by virtue of his training in the interpretation of pathologic changes in tissues and his familiarity with laboratory organization and procedures.

Reference

1. Siegler, Edward: Transactions of the Second Annual Meeting of the Inter-Society Cytology Council, Statler Hotel, Boston, November 12 and 13, 1954, pp. 164-168.

This is the thirty-third in a series of editorial reports sponsored by the Minnesota Society of Clinical Pathologists and designed to foster closer relationships between laboratory physicians and their colleagues. This month's report complements one by the same author that was printed in this section last month. The reader also is referred to the ninth report in this series, which concerned cervical cytology and which appeared in MINNESOTA MEDICINE in October, 1953.

Several weeks ago, a total of 183,000 physicians received pamphlets describing the Cancer Cytology Foundation of America, Inc., which was mentioned by Dr. McDonald. This brochure was accompanied by a copy of the pamphlet called *Spotlight*, published by the Committee for Constitutional Government, Inc. This entire issue of the *Spotlight* was devoted to a discussion of exfoliative cytology under the title "Cancer Cytology is the Discovery of the Century." It is rather curious to see a medical diagnostic procedure being promoted by such an organization.

The American Cancer Society is evaluating Dr. Ayre's Foundation. They point out that pathology specialty groups have been opposed to the establishment of regional centers for cytology because the test is rapidly becoming available to patients and physicians desiring it and because it is important that the closest possible professional relationships be maintained among the patient, the clinician and the pathologists endeavoring to interpret test material. The Inter-Society Cytology Council has gone on record as not favoring the aforementioned Cytology Foundation.

GEORGE G. STILLWELL, M.D.
Chairman, Editorial Committee

DIABETES INSIPIDUS AND PREGNANCY

(Continued from Page 811)

4. In conclusion, diabetes insipidus is a rather infrequent complication of pregnancy, and the disease itself seems usually of obscure etiology.

5. The course of diabetes insipidus during and following pregnancy is rather unpredictable.

6. At least during pregnancy, the preferred treatment seems to be pitressin injections, because of the absence of oxytocic effect.

References

1. Lake, M.: M. J. Australia, 2:206, 1947.
2. Carfagno, S. C.; Durant, T. M., and Shuman, C. R.: Arch. Int. Med., 92:542, 1953.
3. Richter, C. P.: Am. J. Physiol, 110:439, 1934.
4. Soule, S. D.: Am. J. Obst. & Gynec., 33:878, 1937.
5. Blotner, H., and Kunkel, P.: New England J. Med., 227:287, 1942.
6. Fisher, C.; Magoun, H. W., and Ranson, S. W.: Am. J. Obst. & Gynec., 36:1, 1938.
7. Greene, J. A., and Gibson, R. B.: J. Lab. & Clin. Med., 24:455, 1938-39.
8. Carter, P. J.: Urol. & Cutan. Rev., 44:549, 1940.
9. McLaren, H. C., and McLeod, M.: J. Obst. & Gynaec. Brit. Emp., 49:51, 1942.
10. Maranon, G.: Brit. M. J., 2:769, 1947.
11. Tannenbaum, A. J.; Bertling, M. H., and Burwell, J. C.: Am. J. Obst. & Gynec., 63:472, 1952
12. Hickey, R. C., and Keettel, W C.: Surg., Gynec., & Obst., 98:541, 1954.

Editorials

JOHN F. BRIGGS, M.D.
ARTHUR H. WELLS, M.D.
HENRY G. MOEHRING, M.D.

PHYSICAL MEDICINE

Physical medicine, in a large measure, is concerned with the treatment of chronic diseases or disabilities in which recovery may be long delayed. As such, it has frequently been neglected by the general practitioner who is busy with acutely ill patients. Yet, it has been estimated that up to 40 per cent of clinical visits are for conditions which need treatment by physical therapy.

Physical therapy to traumatic injuries, arthritis, neurological disabilities and other conditions, when they are first seen, accelerates recovery and helps to prevent the development of a chronic disability. The methods which can be used in an office for treatment of these conditions should be a part of the armamentarium of every general physician.

Approximately one-fifth of the patients in general hospitals need treatment by physical medicine. Patients who remain in bed for any length of time show progressive deterioration of the cardiovascular system, progressive weakening of the muscular system, demineralization of the skeletal system, development of contractures, and loss of motivation to be independent. Of all these, loss of motivation is the most serious, for without motivation to be independent no patient can be successfully rehabilitated. When patients must remain in bed for prolonged periods, a program of activity should be planned commensurate with their capacities. Occupation therapy provides medically supervised activities at any energy level to maintain the patient physically and mentally. The nurses should maintain the range of motion of all of the joints and supervise posture to insure that contractures do not develop. Physical therapy with all of its forms of treatment hastens recovery and prevents deterioration of the patient. The patient should be taught and required to do for himself the activities of which he is capable. These include independence in moving in bed, eating, getting out of bed, moving from chair to chair, dressing, standing and walking. The longer the patient remains dependent, the more difficult is it for him to re-establish independence.

The goal of medical practice is to restore all patients to health as completely and quickly as possible. Physical medicine provides some of the tools necessary to achieve this goal.

FREDERIC J. KOTTKE, M.D.

PSYCHIATRIC CONSULTATION IN SOCIAL AGENCIES

Social agencies give many tangible services to families and individuals, such as financial assistance, homemaker service and child placement. But if there is severe stress in family relationships or if any family member is seriously at odds with others or with himself, both the need and the service required are less tangible.

Whenever such a situation comes to the attention of a social agency, the social worker seeks to determine whether or not the person or family in question has enough social adequacy and personality strengths to use counselling, a child guidance approach, or such other forms of a helping relationship as may be appropriate. Much of the skill of the social worker has been developed in this area of relationships. If it is found that the client cannot enter into a meaningful and constructive relationship with the social worker, questions as to the precise nature of his emotional problems and personality structure demand thorough-going attention. It may be that the client is mentally ill or severely neurotic or has a deep-seated personality problem. With a clearer understanding of the behavior of such a client and of his family relationships, the social worker may be able to give the correct kind of support and guidance to him and to his family. Or, referral to a private psychiatrist, a mental hygiene clinic or a hospital providing psychiatric care and treatment may be the only service the social agency is equipped to offer.

To clarify these problem situations, social agencies have developed the practice of employing a psychiatrist, usually on a part-time basis, to give consultation to members of its staff, as need arises. The social worker presents the problem case in detail to the psychiatric consultant,

Third in a series of editorials on Family Service.

and the handling of it to date is discussed. Ordinarily, the psychiatrist does not see clients. He evaluates the worker's experience with the case and contributes his understanding of psychiatric elements appearing in the total situation as it is presented to him. He may support a continuance of the existing plan of social treatment or suggest changes. He may point out that, from the social history, it appears likely that a certain member of the family is mentally ill and recommend a psychiatric examination. In all cases presented to him, the psychiatrist acting as consultant provides certain safeguards, professional guidance and rich learning opportunities for the staff of the social agency in directions extending beyond their proven areas of competence.

KATHERINE H. TINKER, *Supervisor*
Family Service of Saint Paul

SEPARATE FUND-RAISING

The established policy of the volunteer Board of Trustees of the National Foundation specifies that a separate March of Dimes is the only public appeal for funds to finance the work of the organization. The 3,100 local chapters of the National Foundation are required by charter to adhere to this policy of separate fund-raising and may not participate in any joint, united or federated fund-raising activities, or accept any funds raised by this method of solicitation.

Joint, united or federated fund-raising is interpreted by the National Foundation as any single solicitation of funds within a community, plant, institution or organization for the benefit of more than one organization.

There are six basic reasons for this National Foundation policy of separate fund-raising:

1. *Public Awareness.*—The recent tremendous advances in the field of polio prevention would not have been possible without a separate March of Dimes. Better than anything else, the March of Dimes tells the story of polio to the American people, helps make them aware of polio and educates them to fight the disease. In any joint type of fund-raising, the polio problem might lose the attention it deserves and the conquest of the disease might be postponed for years.

2. *Fluidity of Funds.*—A separate March of Dimes is essential because conditions all over the country have to be met as they arise and this requires a complete mobility of funds, equipment and personnel. In any joint fund-raising, local committees—unfamiliar with the complex nation-wide activities of the National Foundation—would pass upon its annual budget. Any arbitrary regulation of expenditures — which would be inevitable under a federated fund-raising program—would hamper continuation of the National Foundation's long-term research and professional education programs.

3. *Opportunity.*—A separate March of Dimes offers an individual a chance to be a part of a great humanitarian program at a very small cost. A dime or a dollar is a trifling sum in itself but, given a nation-wide drive, this same dime or dollar helps sponsor research that may mean the end of a crippling disease. Multiple drives offer an individual a variety of opportunities where his small sum can do a great good. If a person does not choose to take the opportunity to do good, he need not give.

4. *The American Way.*—A separate March of Dimes is based on the American tradition of freedom of choice. Each January, Americans have the right to endorse or withhold their support from the March of Dimes on the basis of their approval or disapproval of its program. Last year, about 75,000,000 Americans chose to contribute to the fight against polio. It also is in keeping with the American tradition that each organization should be free to decide whether it will join any federated or group fund-raising program.

5. *Volunteers.* — Each separate drive draws upon civic-minded citizens for volunteers; a separate March of Dimes gives an individual a worthwhile activity in which he can participate along with neighbors. This is perhaps the most effective picture we have of democracy at work at the grass-roots level. Many March of Dimes volunteers serve throughout the year, aiding families and communities hit by polio. Volunteers from the Mothers' March on Polio helped make the Vaccine Validity Trials of 1954 successful by aiding doctors, nurses, teachers and health officers. Joint fund-raising narrows community participation in welfare, reduces opportunities for volunteers and closes valuable avenues of leadership.

6. *Success.*—In 1938, the public gave the first separate March of Dimes a gross of over $1,500,000 to fight polio. In 1954, it gave a separate March of Dimes a gross of $55,000,000 for a comparable drive. This is an unprecedented accomplishment for a truly voluntary health agency—not because of the amount raised, but because of the vital work that this money made possible. The National Foundation does not exist to raise money—it raises money to exist so that it may carry on its work. The National Foundation, now on the threshold of conquering a crippling disease, cannot abandon this successful method of separate financing.

DESIGN AND DECORATION FOR THE DOCTOR'S OFFICE

With a few pleasant exceptions which, happily, are increasing in number, doctors' offices have never been noted for relaxing comfort and good taste in interior design, color and furnishings. One might almost say that these elements are out-dated only by the magazines on the reception room table.

Because most people who go to doctors' offices are disturbed and would rather be some place else, it would seem that making them as comfortable and happy as possible while there would be to show not only decent consideration but also good business sense. Most would rather build themselves up for a visit with an Albert Schweitzer than a Torquemada.

The doctor's office is a problem in design and decoration which involves skilled diagnosis and treatment by a professionally trained person. Turning it over to your receptionist, your office assistant, or even your wife—because it needs the well-known "woman's touch"—is tantamount, generally speaking, to turning over a lobotomy to the pharmacist at the hospital.

The doctor's office is not "home" to anyone; it is a semi-public, professional premise and it should be treated as such in matters pertaining to style and color. There is a firm and significant trend towards what is known as "contemporary" design in the decoration of business and professional offices. The fact that you and most of your patients may live in houses that you fondly imagine are "period" or "traditional" in style may be all the more reason for "going modern" in your office. Contemporary design need not be mechanistic, impersonal, sterile or coldly clinical—epithets which have been leveled at it by the nonunderstanding. It *can* be warm, inviting, stimulating—and good advertising, as well. (Advertising, being by definition a four-letter word, how did it get in here? Let's just say it's nice if people notice your pleasant office the way they notice your "bedside manner" and tell other people about it.)

Color, whether used for purely decorative appeal or, more purposefully, as a very functional tool, has assumed tremendously increasing importance in recent years. Although medical literature contains many references to color therapy, these are perhaps to be heavily discounted. But as to its psychological and emotional effects on people, enough is known to allow us to put it to good use in business and industrial situations. One would be reactionary, indeed, to ignore its functional possibilities and continue to treat it merely as pretty to look at. A well-integrated interior design job in the doctor's office calls for a working knowledge of the effects of color on people psychologically, as well as aesthetically.

The successful doctor is not the one who hung up his diploma five years ago, or twenty, and then forgot about studying and learning any more. It's competition, as well as a thirst for improvement that keeps him reading, attending lectures, going to conventions and constantly striving to improve his techniques. Many will hesitate to admit the existence of competition in the professions, but it's there. Some businesses—banks, for example—used to feel it undignified to go after business aggressively. Now, they're merchandising to the limit the services they offer. It may not be amiss for the doctor to divest himself of the "better mousetrap" psychology and begin doing a little merchandising.

One way he can, within the framework of professional ethics, is to make his place of business look like a good place to come to and feel like a nice place to be.

CLARENCE DEUTSCH
Color Counselor

ANCILLA, -AE, *f. dim.*

What with all the energy expended to make meanings clear, or to slant words, phrases, sentences, and whole books, we were pleased to have cognizance taken of the misuse of *ancillary** in a current issue of *The Journal of the Medical Society of New Jersey. Ancilla* is a diminutive of a Latin noun meaning servant, specifically, maid-servant. In its evolution into our word *ancillary,* all that might be pejorative has survived in most current usages, and none of the faithfulness or other desirable characteristics of a good maid-servant remains. The tag *ancillary services* thus becomes tinged with servility, if not the scullery.

Decades ago someone relegated the practice of anesthesiology, pathology and radiology to this scullery with the inept complaint that the "faculties of the physician were being subordinated to the ancillary services. . . ." Perhaps he was wroth and used ancillary to express his meaning precisely, but the phrase stuck, despite the physical removal of laboratories from the cellars and attics of medical installations to central locations, and the development of these specialties into necessary parts of the modern practice of medicine. Unfortunately, these specialties have remained ancillary in the thinking of some poorly informed folks; e.g., in the current dispute between Iowa physicians and Iowa hospitals, a Dr. Letourneau has tried to uphold the hospital's proprietary interests in the practice of anesthesiology, pathology and radiology by testifying that pathology and radiology are not the practice of medicine, but are only fact-gathering methods (one of the bitterest jokes in teaching x-ray departments the country over is the widespread impression among laymen that x-ray examinations take all the guess-work out of diagnosis)!

Of necessity, various specialties in medicine must play secondary roles when circumstances require it. The patient consults *his* physician and from thenceforth, all other physicians consulted are auxiliaries, though not subsidiaries. The patient's physician is the one who integrates the diagnostic and therapeutic parts other physicians play in the solution of that patient's problem. Such a procedure is simply the day-in and day-out cooperation for the welfare of the patient at the foundation of medical ethics. However, a secondary role whenever the circumstances require it, and the rendition of only ancillary (we remind you, ANCILLA, -ae, *f.*: Maid-servant) services are vastly different. And to be labeled thusly by confreres is doubly derogative.

You are not affected, you think; but if any group of physicians gets lost in the welter of non-physicians' trying to dominate the practice of medicine, we all lose. We could do no better than to end this lament the same way Dr. Demy ended his erudite comments, with the Devotion of John Donne:

> No man is an Iland, intire of itselfe; every man is a peece of the Continent, a part of the maine; if a Clod bee washed away by the Sea, Europe is the lesse, as well as if a Promontorie were, as well as if a Mannor of thy friends or thine owne were; any man's death diminishes me, because I am involved in all Mankinde; and therefore never send to know for whom the bell tolls; it tolls for thee.

H.G.M.

*Demy, Nicholas G.: The Ancillae, J. Med. Soc. of New Jersey, 52:419, Aug., 1955.

In Memoriam

JACK FRIEDMAN

Dr. Jack Friedman, Minneapolis radiologist, died September 29, 1955. He was clinical assistant professor of radiology at the University of Minnesota and a radiologist at Mount Sinai Hospital in Minneapolis. He was forty-four years old.

Dr. Friedman attended the University of Illinois College of Medicine and interned at Lutheran Deaconess hospital in Chicago. He took postgraduate work in radiology at the University of Minnesota.

A member of the Hennepin County Medical Society, the Minnesota State Medical Association and the American Medical Association, Dr. Friedman also belonged to the American College of Radiology, the Radiological Society of North America, the American Roentgen Ray Society, and Sigma Xi. He was a member of Temple Israel.

He is survived by his wife, Dorothy, and his daughter, Elizabeth, Minneapolis; his parents, Mr. and Mrs. Louis Friedman, Chicago; two brothers, Irving and Leon, and a sister, Adele, all of Chicago.

President's Letter

SOMETHING GOOD

At this time of year, when America's bounty should make us very thankful, I feel it appropriate to quote something said by one of our elder statesmen, Herbert Hoover, on his eighty-first birthday:

"During the last score of years our American way of life has been deluged with criticism. It comes from our own people who deplore our faults and genuinely wish to remedy them . . .

"Criticism comes daily from the habit of our political parties to deplore the opposition. It arises from the forthright refusal of the American people to wash their dirty linen in secret. It comes from our love of sensational incidents where villainy is pursued by law and virtue triumphs . . .

"Altogether, if we look at the criticism alone, we seem to be in a very, very bad way and engaged in our decline and fall.

"But we should lift our eyes unto the hills from whence cometh our help. We should occasionally mention something good about ourselves.

"We could point out that our American way of life has perfected the greatest productivity of any nation on earth; . . . We could point to our constantly improving physical health and lengthening span of life. We could point out that the mechanical genius of our people has, by millions of labor-saving machines, taken the sweat from the backs of most of our people.

"In the governmental field, we could suggest that our supposedly decadent people still rely upon the ballot and the legislative hall to settle their differences without a secret police with slave camps.

"In the cultural field, we could point out that, with only 6 per cent of the world's population, we have more youth in our institutions of higher learning than all the rest of the world put together. We could probably enumerate more libraries and more printed serious words than all other 94 per cent of the earth put together.

"On the moral and spiritual side, we have more hospitals and charitable institutions than all of them (the nations). And we could suggest that we alone, of all nations, fought in two world wars and asked no indemnities, no acquisition of territory, no domination over other nations.

"We could point to our advancement of the spirit of compassion. We could prove it by the billions of dollars we have made as gifts to save millions from famine and governments from collapse.

"Much as I feel deeply the lag in giving an equal chance to our Negro population, yet I cannot refrain from mentioning that our 14 million American Negroes own more automobiles than all the 200 million Russians or the 200 million Negroes in Africa.

"All of which is not boasting, but just fact. And we could say a good deal more.

"What does all this mean? It means that freedom of mind, of spirit and of initiative still lives in America. It means that our people are strong in religious faith. Here alone are the open windows through which pours the sunlight of the human spirit. Here alone, even with all its defects, is human dignity not a dream but an accomplishment.

"These ideals of freedom and religious faith guarantee there will be no decline and fall of American civilization."

Yes, we have much for which to be thankful.

Arnold O. Swenson

President, Minnesota State Medical Association

Medical Economics

Edited by the
Committee on Medical Economics,
Minnesota State Medical Association
George Earl, M.D., Chairman

SURVEY SHOWS PUBLIC LIKES M.D.'S

The public generally likes Doctors of Medicine and understands the problems facing the profession today. This was brought out recently by a public opinion survey sponsored by the Los Angeles County Medical Association. The poll was conducted this summer.

The survey showed that doctors as a group enjoy a position of confidence and respect. According to a recent report in *The Bulletin of the Los Angeles County Medical Association*, "this finding differs markedly from the results of other recent opinion samplings carried out in scattered areas of the nation which indicated widespread 'public hostility' toward the medical profession." The survey was based on interviews with 360 adults in Los Angeles County.

The Bulletin article points out, however, that there are many areas in which the public has insufficient information and others in which medical public relations could be improved. But, one compelling fact emerges from all the data, the report states: The public is *not* dissatisfied with physicians and their services today!

The Bulletin quotes one interviewee as saying:

". . . doctors didn't invent sickness and misery. I think they are doing their best to do a job that has to be done. They are in a tough spot to have good public relations. Their 'customers' just don't *want* to buy what they are selling at any price. Even if doctors could fix broken legs for a dime a dozen, no one would want to have one. Nobody likes to be sick. And many people—when they get sick—get sore and take it out on the doctor."

Other important findings were:

1. 75.1 per cent had a regular or family doctor.

2. 91 per cent stated that the last time they had seen a physician he had made entirely clear all that they wanted to know about their illness.

3. 95.2 per cent felt that the M.D. had given them all the time they needed for diagnosis and treatment.

4. 85.5 per cent called the doctor's attitude toward them, "kindly, sympathetic," and definitely not calloused or impersonal.

5. More than half, 54.3 per cent, had changed physicians because of dissatisfaction. And the principal reasons for dissatisfaction were, in order of their frequency: "Not thorough;" "Didn't like his medication;" "Not a specialist;" "Charged too much."

6. 77.5 per cent believed that an osteopath is a medical doctor who has specialized.

7. 83 per cent of the public confused internists with internes.

8. 35 per cent had undergone surgery in a Los Angeles hospital.

9. 76.5 per cent believed that all doctors would make night or Sunday calls if humanly possible.

10. Only 15 per cent of those who called a physician in Los Angeles found he couldn't take the case. And 61.3 per cent of this group were of the opinion that the doctor was doing his best but was just too busy.

11. When patients were referred to doctors other than their own in emergencies, 70.8 per cent were entirely pleased with the substitute and 26.1 per cent stayed on with the new physician.

12. 86.5 per cent were positive that physicians never undertook procedures they were not qualified to perform but always referred patients to appropriate specialists.

13. The public generally was of the opinion that "all" doctors were more competent to diagnose different diseases than to perform different surgical procedures.

14. 64.2 per cent rely on the recommendations of a friend in selecting a physician.

15. Most persons were lenient about waiting for the doctor to keep his appointment. 82.8 per cent felt the M.D. was justified in running behind schedule in his appointments while 10.5 per cent thought this was "unreasonable." 22.6 minutes was the mean amount of time the respondent expected to wait. 4.3 per cent considered an hour or more "usual."

16. Based upon their own personal experience, 88 per cent were entirely satisfied with physicians' fees. However, 30.2 per cent were of the opinion

that medical fees "generally" are "unreasonable." The reason most often given for this was, "The average working person can't afford the fee."

17. 74.3 per cent were more interested in having their hospital bill covered by insurance than in having the doctor's fees covered. This percentage rose to 86.4 per cent with community leaders and influence groups.

18. 74.8 per cent had the doctor's professional education pegged right—eight or more years of study.

19. 76.4 per cent were sure that they had far more leisure than an M.D. 73.4 per cent felt that doctors worked harder than they did.

20. 50.2 per cent are of the opinion that doctors send their patients to particular pharmacies. And 33.9 per cent think that the physician gets a "rebate" from the pharmacy.

21. 83.7 per cent praised the medical profession for informing the public regarding "new methods, treatments and medicines."

22. 82.1 per cent wanted no part of compulsory health insurance. The percentage went up to 91.5 per cent with the influence group.

23. 59.8 per cent preferred "service type" insurance. 28.8 per cent wanted "indemnity." 7.4 per cent like "closed panel" coverage.

24. 70.1 per cent want itemized bills and 77.8 per cent prefer a letter to a phone call as a reminder for a delinquent account. 37.9 per cent considered it completely unjustified to have delinquent accounts turned over to a collection agency.

The questions in the survey were asked of two groups—the general public (309) and the influence group (fifty-one). The influence group was selected arbitrarily to represent as nearly as possible a cross section of those persons whose position put them in a category of leadership. They included representatives of labor, social groups, teachers, clergy, business and industry, State assemblymen, State senators, city councilmen, and the Los Angeles Board of Supervisors.

AMA STUDIES MEDICAL CARE ECONOMICS

A recent issue of *The Journal of the American Medical Association* reports on a review of the economic position of medical care over the past quarter century made by the Bureau of Medical Economic Research.

According to an AMA editorial, "The findings emphasize the 'middle ground' position of the medical care 'industry' during that period, 1929-1953, when gross national product rose from 104 billion to 365 billion dollars and personal consumer expenditures rose from 79 billion to 230 billion dollars." The editorial continues:

> "While dollars expended for medical care followed the over-all pattern of expansion, the Bureau notes that since 1930 the percentage of personal consumer expenditures going for medical care varied only slightly, from 3.99 to 4.35. Since World War II, however, the percentage has risen at a more rapid rate, from 4.14 to 4.35."

Effect of Birth Rate

One factor that increased personal consumer expenditures for medical care, in dollars and as a percentage of the total, the editorial says, was the tremendous upswing since World War II in the number of births and the birth rate. The increased number of babies and young children has affected not only hospital and obstetric expenditures but has increased the demand for other medical services, since this youngest age group normally requires the most frequent medical attention. The editorial notes this effect:

> "In the long run, of course, this imbalance will be corrected as today's toddlers become tomorrow's productive adults. Moreover, the reduction of the maternal mortality rate to a very low level has contributed to the high birth rate by reducing the mortal fear of childbearing almost to the vanishing point. The economic effect of the 1,200,000 increase in births from 1945 to 1953 has been obscured by statistics that do not show a division of medical expenditures into those for childbearing, disease, and accidents. Without such a breakdown, it is easy to misinterpret the increase in medical expenditures by ascribing it to a decline in the health of the American people or a disproportionate rise in medical care costs."

Second Factor Isolated

The editorial goes on to say that the Bureau study has isolated as a second factor responsible for the increase in expenditures the item "medical care and hospitalization expense." These expenditures represent premiums less claims paid; this difference is primarily overhead cost. "The rapid growth in voluntary health insurance has resulted in an increase of 779 million dollars in this insurance overhead item from 1929 to 1953; this amount represents one-ninth of the total 7,064 million dollar increase for all medical care items. The

increase in overhead costs is, of course, a price that must be paid for the rapid extension of voluntary health insurance."

Prices Studied

The index for medical care and drug prices was studied for this period. In 1954 it stood at 173.9, the period of 1935-1939 equalling 100. This is well below the 191.9 for the entire index, based on the U. S. Bureau of Labor Statistics' Consumer Price Index. And, the editorial continues, the item indexes for physicians' and dentists' fees were still lower—160.3 and 174.5. "The only component of the total medical care and drug index that showed a marked rise, the editorial states, "was hospital room rates, which was 322.1 in 1954. If the upward effect of this component were eliminated, the over-all medical care and drug index would be still lower."

Reporting on the physician's share in the medical care dollar, the editorial says that a dollar spent for medical care in 1953 was not divided among the suppliers of these services and commodities in the same way as was a 1929 dollar. It states:

"The 33 cents that the physician received in 1929 dwindled to 28 cents by 1953; the share of the dentist and that for drugs and sundries also declined. The compensatory increases were for all other medical care (which includes the rapidly growing insurance overhead item) from 17 to 20 cents; and for hospitals, from 14 to 26 cents. If these trends continue, the hospitals' share will exceed the physicians' share by 1960."

Rise in Productivity

Output per physician has risen, the editorial notes, but this has counterbalanced the lag in physicians' fees and the decline in the physicians' share of the medical care dollar. Thus, the effective supply of physicians' services has increased much more rapidly than the number of physicians, the editorial emphasizes. "Also, seeing a decreasing percentage of patients in their homes has resulted in a saving of the physician's time. Use of more auxiliary personnel in his office and in the hospital and use of more effective drugs have also been major factors in increasing the technological efficiency of the physician. As a result, the average income of physicians rose at almost exactly the same rate as the average earnings of all wage and salary workers over the period. . . . The incomes of physicians and their patients continue to keep pace.

Efficient Industry

Noting these over-all trends and their effect on the over-all medical care picture, the editorial concludes:

"The various providers of services and commodities in the medical care 'industry' can well be proud of a quarter century record that included great medical advances—the increased life expectancy at birth, the declines in infant and maternal mortality, and the development of new drugs and treatments—while little change occurred in the industry's relative economic position. Possibly this is our most efficient industry!"

AMERICA CALLED MEDICAL MAGNET

A recent news release from the American Medical Association states that the United States has become a "medical magnet" for physicians in Europe, Asia, Africa, and Latin America.

"More than 5,000 foreign physicians came to this country during the year 1954-55 for study," the release says. This information was brought out in a survey by the Institute of International Education and the American Medical Association.

The survey notes that the physicians came from eighty-three different countries for internship and residency training at hospitals in forty-two states, the District of Columbia, Hawaii, Puerto Rico, and the Canal Zone. Those countries sending the most doctors to America were the Philippines, Canada, Mexico, Germany and Turkey.

Resources Checked

The survey reported that more than 2,000 of these physicians were in the United States on their own resources. Others were sponsored by at least sixty-seven different agencies, including their own or the United States government, the United Nations, and religious, educational or philanthropic organizations. Many were sponsored by the hospitals in which they were training.

The survey also notes:

"In addition to the large number of physicians in hospital internship-residency training, others visited this country as observers, professors, or guest participants in research. They represented 21.5 per cent of all foreign educators who visited the country during the year.

"In comparison, only 3.6 per cent of all American educators visiting other parts of the world in 1954-55 were listed under medicine."

The Dean's Page

THE FALL SEMESTER BEGINS

The Medical School has started upon another year's activities. One hundred and twenty-eight new students have enrolled as freshmen and four new students have been accepted into the junior class as transfers from other medical schools.

One half day at the opening of the year was devoted to a program of Welcome and Orientation for the freshman students. Talks about the Medical School and about the opportunities and obligations of medical students were given by the Dean and by the Assistant Dean, William Maloney; Dr. Cecil Watson, Professor of Medicine, spoke on "The Relation of the Basic Sciences to Clinical Medicine"; Dr. Donald Hastings, Professor of Psychiatry, on "The Personal Relationship of Student, Physician, and Patient"; senior student Ralph Swanson discussed medical student activities and the Medical Student Advisory Council; and senior student Duane Flogstad spoke on "The Student American Medical Association."

After a break for coffee and sociability, the freshman students reassembled in the Mayo Memorial Auditorium with the students of all other classes, members of the faculty and of the Minnesota Medical Foundation. Dr. Wesley Spink, President of the Minnesota Medical Foundation, presided at this assembly and presented scholarships to six freshmen, five sophomores, seven juniors, and three seniors. These scholarships were provided by the Minnesota Medical Foundation, and were awarded on the basis of financial need and of promise as a successful medical student and physician. Until a few years ago, the University of Minnesota offered no scholarships for medical students. Today, these scholarships are proving invaluable in enabling a group of well-qualified young men and women not only to study medicine, but also to profit by the opportunities for a medical education which are available to them.

Following the presentation of scholarships, the Dean spoke on "Health as an Instrument of International Policy." Immediately following the adjournment, the Minnesota Medical Foundation held its annual meeting at a luncheon in the Junior Ballroom of the Coffman Memorial Union.

The orientation program for freshmen and the general Medical School Assembly constituted a splendid and thrilling beginning for another year of effort and achievement on the part of students, faculty, and friends of the Medical School. The construction of the Mayo Memorial Auditorium makes possible these assemblies which are of inestimable value in fostering student-faculty team work and esprit de corps in the Medical School. I only regret that all of the physicians of the state could not have shared this splendid occasion with us.

HAROLD S. DIEHL
Dean, The Medical School
University of Minnesota

Letters ▲ ▲ ▲

Dear Editor:

The other day I ran into an abstract of an original paper in MINNESOTA MEDICINE, 37:862, 1954, by Dr. R. E. Semsch. The paper recommends a universal antidote for children, the preparation consisting of charcoal, two parts, magnesium oxide, one part, tannic acid, one part. I would like to call your attention to two matters with regard to this formula which should not be given such widespread publicity without considering the scientific facts.

Charcoal varies enormously in its adsorptive properties. Perhaps in the full paper, the author describes the type of charcoal to be used, otherwise the statement "charcoal" is meaningless. The second or major part of my criticism is that the author compounds two incompatibles, magnesium oxide and tannic acid. It is elementary chemistry to know that these two compounds react promptly to form magnesium tannate and I have not taken the trouble to determine the amount of magnesium oxide which would be left over after the interaction of these two chemicals, but it is obvious that there would be no tannic acid. Instead, the author's mixture would contain charcoal, magnesium tannate and magnesium oxide, and therefore it is entirely improper for him to state that the tannic acid will precipitate alkaloids, glucosides and some heavy metals. Perhaps magnesium tannate will do so, but this would have to be proved in the laboratory.

The only reason I am writing this letter is in the interest of scientific accuracy, for the type of loose statement used in the paper is not in accordance with established facts in chemistry. After all, when one mixes hydrochloric acid and sodium hydroxide, one loses entirely the properties of one or the other compound, or both, depending upon which is in excess. The chemical reaction produces common salt, which is of course entirely unlike the chemicals from which it is formed.

Very truly yours,

HERMAN H. KAHLENBERG, PH.D.

Sarasota, Florida
October 3, 1955

* * *

Dear Editor:

Summer vacations offer the physician in practice a chance to muse about events during the year preceding, and no event will be mused upon by more physicians than the coming of the Salk vaccine against poliomyelitis. Beclouded though the subject is at the moment, there is ample reason to believe that the doubts will be settled and the questions will be answered, and within a reasonable time the new tool will take its place in routine practice.

The raising of such doubts and questions in the first place, as they have been raised in the press and in the minds of the public leads the muse a little further, though, and the doctor finds himself assuming a posture of distressed dissatisfaction with some parts of the situation. Furthermore, he senses that his posture may easily be misunderstood by the same American public which at first demanded the vaccine in a hurry, and then began to telephone family doctors to find out if the vaccine was safe. It would take only what the press agents call a small "switcheroo" to make the doctor the fly in the public's ointment at the present time. One's comments about such a "hot" subject had better be circumspect if they are likely to be quoted from one patient to another. Now, how is it that this situation came to be?

To come to the point quickly, this is the first time that public demand for a medicament has ever been created by such a large and careful campaign of press releases. The campaign was started before the medicament was manufactured, before it was tested for safety, before scientific information concerning it was published in professional journals. But these are really minor breaches of good medical policy. The doctor wonders if it is right to advertise any remedy. It never has worked well for the public interest in the past. Should there have been any campaign of press releases in the first place? Doesn't such a campaign remove the element of professional judgment from the administration of the injections? The answer is "yes" of course, and we still do not know enough about the material to know whether a small grain of professional judgment ought not enter the decision to use the vaccine. A highly intelligent cancerophobe asked the writer whether Salk vaccine sensitized one to monkey kidney. If it did, he wanted none, for future cancer therapy (for his as-yet nonexistent cancer) might thereby be proscribed for him.

The only justification for such advertising of a medicament that occurs to one readily is that it is required in order to get a testing situation set up which will contain the needed number of individuals. This is not the case here, for the testing supposedly is finished, and was going on when the campaign started. One must conclude that the press releases were not required by the scientific part of the situation.

One muses along a bit farther to the realization that the National Foundation for Infantile Paralysis conducted its publicity campaign in order to raise money which has been used for polio care and for polio research. Both are blameless causes. Both have been helped by advertising a not-yet-ready vaccine. But does this justify advertising a medicament? Bear in mind that the free advertising via press releases was voluntarily sought out by the National Foundation. But remember also that this is not a single doctor and not a medical society, and therefore not governed as doctors and medical societies are governed by an ethical code which forbids advertising. There has been no ethical breach. The National Foundation merely has to follow its own rules and the laws under which it was incorporated; it is not subject to a code of ethics. It is not practicing medicine though there are those who now are questioning this point. Actually the conduct of a sizeable chunk of medical practice in 1955 has been deter-

mined by the policy of the National Foundation. The Foundation has created a situation in which thousands of doctors have injected millions of children with a substance to them unknown. No one need quibble about its being unknown; the unexpected cases of polio which followed its use proved that it was unknown.

The present events are not the first which have arisen as a result of the National Foundation for Infantile Paralysis. In 1953 the Foundation promoted gamma globulin with equal energy, enlisted co-operation of the Red Cross and health departments, and spent a large sum of money on a tool which we know now to be of little value. It could have been shown useless without trying it out on a national scale, and the money could have been saved. The same sense of urgency filled all the press releases in 1953 as have been noted in 1955. It may be rememberd by some that the Foundation has had previous experience with vaccine as well. It is an experienced agency as well as a large and rich agency. Its performance with Salk vaccine probably may be regarded as what one should expect from such a quasi-medical, quasi-public agency.

Thus one muses along some more and into the field of the relationship of the practicing doctor to such agencies. They exist in some numbers. They have large funds, some of them to be spent for what is called education. Other terms for education in this sense are "public relations," "lobbying," "public education," and the providing of "educational materials." We have before us now an example of the way such public education may go astray.

These medical foundations will continue to award research grants, and we now know, will take research results direct to government units for testing in the field as well as for distribution. We now know that they will drop responsibility into the lap of the Federal government if the going gets rough or if controversy arises. They are subject to technical medical guidance, usually of the most brilliant caliber. But what is the relation between the practicing doctor to these agencies? Is there a way for the practitioner to steer agencies like these away from pitfalls like premature advertising which he has known for generations to be a pitfall? Would the suggestions of the practitioner be welcome, and would they be heard?

Individual participation by thousands of doctors in hundreds of organizations, agencies and Foundations seems not to work, and a priori it is impractical. Opposition to the agencies is not only not in the public interest, but futile. They include in membership, great numbers of earnest, well-educated, serious people of the greatest integrity. The difficulty seems to be that they have a propensity for gigantic boo-boos which are also not in the public interest. These arise because agencies are not accustomed to medical practice, and their good works require medical practice to be applied.

Where does the answer lie, then? It must be admitted that the answer isn't new: the relation of agencies to practicing physicians must be a function of the American Medical Association, the State Medical Associations, and the County Medical Societies. The change which might make medicine's efforts more fruitful is to take the initiative. Make the county societies' programs more topical and discuss the policies of the local units of the agencies, as well as the national policies. Stir up the inactive State committees to go and deal with the Foundations that they were appointed to treat with. In the national AMA offices, raise more money from the membership so that more national officers can take a year away from practice and travel the country and counsel with and advise Foundations, agencies, and quasi-medical organizations. These groups are a part of the medical picture in the American community, and all the practicing doctors must learn where they fit, what they can do, and how they can be helped. If we are to avoid another premature release or other miscarriage of effort from this or another agency, we must take our money in dues and assessments and use it to carry the suggestions and advice of practicing physicians to the agencies.

Organized American medicine must share in the blame for the polio vaccine embarrassment. We in practice should have pressed our advice harder. If it seemed unwelcomed by the National Foundation for Infantile Paralysis officials, the same team should have taken the same time and money and brought the advice to the physicians instead, so that when the vaccine was announced the doctors who have to administer it would have known pretty well what they were to handle.

This is only the first episode of the sort on this scale. A good blood or urine test for cancer may turn up tomorrow. Will we be ready to show our investigative colleagues how it may be applied best for the good of man? More people fear cancer than fear polio.

HERBERT PLASS, M.D.

Minneapolis, Minnesota
August 27, 1955

* * *

Dear Editor:

We have read with interest your letter to Mr. Elder of our St. Paul District Office dated June 7, 1955, in which you comment as to the need for standardization of medical report forms being used by an increasing number of agencies.

Your observations in this matter are of special interest since we have been actively engaged in analyzing medical report forms with representatives of life insurance companies, State medical societies, and with a Medical Advisory Committee appointed to assist the Social Security Administration in the formulation of sound medical standards for the evaluation of disability. The focus of these deliberations has been toward a standardized form that will elicit a minimum of essential medical data with the least drain on the individual physician's time.

As our negotiations with these interested groups continue and as we gain further experience with the medical report form currently in use, the whole matter will come up for reappraisal by the Medical Advisory Committee in the fall. Because of your expressed interest in this area, we are enclosing a copy of the medical report form and earnestly solicit your comments and suggestions with respect to it. You will note that it has been kept brief but, if properly executed, should provide the necessary medical information.

Since the quality of response to our requests for medical data depends so much on the good will and co-operation of the medical profession, we are considerably heartened by your constructive interest in the program.

Sincerely yours,

ARTHUR E. HESS
Assistant Director
Department of Health, Education and Welfare

Baltimore, Maryland
July 15, 1955

MEDICAL REPORT

(To be completed by Physician, Institution, or Agency)

This form is supplied for the convenience of the applicant and the physician or institution having knowledge of the applicant's disability. In supplying this form, the Bureau of Old-Age and Survivors Insurance does not assume any responsibility for payment of fees for furnishing the information requested herein. If you prefer, you may submit the needed information in another manner, such as a photocopy of your records or a narrative statement. PLEASE INCLUDE SUFFICIENT DETAIL (USING ACCEPTED MEDICAL TERMINOLOGY) REGARDING HISTORY, CLINICAL FINDINGS, AND DIAGNOSIS TO PERMIT A REVIEWING PHYSICIAN TO REACH THE SAME DIAGNOSIS AS REACHED BY THE EXAMINING PHYSICIAN.

(Name) ..... (Social Security Account Number) .....

I. PERTINENT HISTORY

II. CLINICAL FINDINGS—Supporting diagnosis given below (Please include laboratory tests, limitations of motion, and other loss of functions.)

PLEASE DO NOT WRITE IN MARGIN

III. DIAGNOSIS OF DISABLING CONDITION (Please include date of onset of impairment, if known, and whether impairment still exists.)

IV. REMARKS

When did you first see the patient after ..... ? . . . . . (Date)

Please give date of patient's latest medical examination . . . . . (Date)

PRINT OR TYPE NAME OF PHYSICIAN OR ORGANIZATION	SIGNATURE OF PHYSICIAN, OFFICIAL OF ORGANIZATION, ETC. (IF OFFICIAL OF ORGANIZATION, ETC., ALSO INDICATE TITLE)

STREET ADDRESS	CITY	ZONE	STATE	DATE

NOTE: If additional space is required, please continue on reverse or attach separate sheet.

Form OA-D826
(5-55)

16—71050-2 U. S. GOVERNMENT PRINTING OFFICE

(See letter from Arthur E. Hess on opposite page)

Reports and Announcements

MEDICAL MEETINGS

National

American Academy of Obstetrics and Gynecology, Conrad Hilton Hotel, Chicago, December 13, 1955.

American College of Surgeons, sectional meeting, Milwaukee, Wisconsin, February 27-29, 1956.

American Rheumatism Association, Interim Session, National Institutes of Health, Bethesda, Maryland, December 9, 1955.

Association for Research in Nervous and Mental Diseases, Hotel Roosevelt, New York, December 9-10, 1955.

Mediclinics of Minnesota, postgraduate course sponsored by Academy of General Practice of Broward County, Fort Lauderdale, Florida, March 5-14, 1956.

Radiological Society of North America, Chicago, Illinois, December 11-16, 1955.

MEDICLINIC OF MINNESOTA

The first postgraduate course provided by Mediclinics of Minnesota, a new organization, will be given at Fort Lauderdale, Florida, March 5 to 14, 1956. Presented during an eight-day period, the thirty-two-hour course will be sponsored by the Academy of General Practice of Broward County. Credit for the course will be given by the American Academy of General Practice.

Tuition for the course is $50, payable in advance. Reservations must be made early. Further information can be obtained from Mediclinics of Minnesota, 516 Medical Arts Building, Minneapolis 2, Minnesota.

INTERNATIONAL CONGRESS ON DISEASES OF CHEST

The Fourth International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the American College of Chest Physicians, will be held in Cologne, Germany, August 19 to 23, 1956.

The scientific program is now being organized, and physicians who have carried out original work in diseases of the chest (heart and lungs) are invited to send outlines of their studies to Dr. Andrew L. Banyai, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois. Further information about the congress may be obtained by writing to the same address.

SEMINAR IN OPHTHALMOLOGY AND OTOLARYNGOLOGY

The Tenth Annual University of Florida Midwinter Seminar in Ophthalmology and Otolaryngology will be held at the Sans Souci Hotel in Miami Beach, Florida, January 16 to 21. Lectures on ophthalmology will be presented during the first three days, and on otolaryngology during the last three days of the session. All registrants will be invited to the Midwinter Convention of the Florida Society of Ophthalmology and Otolaryngology on January 18.

Among the lecturers at the seminar will be Dr. C. Wilbur Rucker and Dr. Frederick A. Figi, both of Rochester, Minnesota.

NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

The nineteenth annual meeting of the New Orleans Graduate Medical Assembly will be held February 27, 28, 29 and March 1, 1956, with headquarters at the Municipal Auditorium.

Eighteen guest speakers will participate, and the program will include fifty-four discussions on topics of current medical interest, in addition to clinicopathologic conferences, symposia, color television, medical motion pictures, round-table luncheons and technical exhibits.

The assembly has planned a postclinical tour to follow the meeting. On March 2, a party of doctors and their families will leave New Orleans for the West Indies and Central America via plane. The itinerary includes Puerto Rico, St. Thomas, Haiti, Jamaica, Panama and Guatemala, and arrangements have been made for medical programs in the places visited.

Details of the New Orleans meeting and the postclinical tour are available at the offices of the assembly, Room 103, 1430 Tulane Avenue, New Orleans 12, Louisiana.

TAPE RECORDINGS ON HEART DISEASE

A collection of nine reels of normal and abnormal heart and breath sounds recorded on tape has been made available to the physicians in Minnesota. This device to assist in the teaching of clinical auscultation of the heart, complete with high fidelity playback equipment, has been placed in a number of hospitals for use of the medical and intern staffs.

The equipment is on loan from the U. S. Department of Health, Education and Welfare, Public Health Service, and is made available through the Minnesota Heart Association in co-operation with the Minnesota Department of Health. Any medical groups interested in availing themselves of the heart sounds equipment should contact either of the two state organizations.

CONTINUATION COURSE

The University of Minnesota will present a continuation course in *Obstetrics for General Physicians* at the Center for Continuation Study from January 5 to 7, 1956. The course will be presented under the direction of Dr. John L. McKelvey, professor and head, Department of Obstetrics and Gynecology.

General Interest

Dr. W. H. Halloran, Jackson, is the new president of the Southern Minnesota Medical Association. Elected as vice president of the organization at the group's annual meeting this fall was **Dr. Leo R. Prins,** Albert Lea. Named as secretary-treasurer was **Dr. G. R. Diessner,** Rochester.

* * *

Dr. Merrill D. Chesler, Minneapolis, was the principal speaker at the eighth annual banquet of the Public Health Nursing Service for Cottonwood County, held at Windom on September 13. His talk on "Reconstructive Surgery for Congenital Deformities" was illustrated by color slides.

* * *

Dr. and Mrs. C. L. Oppegaard, Crookston, left on October 8 for Chicago where Dr. Oppegaard attended a meeting of the American Academy of Ophthalmology and Otolaryngology. While in Chicago he represented the Council of the Minnesota State Medical Association at a meeting with the legal branch of the American Medical Association. During the week of October 16 Dr. and Mrs. Oppegaard flew to Mexico City for a tour of clinics and hospitals, and returned to Crookston on October 24.

* * *

Dr. Frances Elizabeth Schaar, Minneapolis, was certified by examination as a diplomate of the American Board of Pediatrics in Chicago recently.

* * *

Named as president of the Northern Minnesota Medical Association at its annual fall meeting in Bemidji was **Dr. L. F. Wasson** of Alexandria. He succeeded **Dr. W. W. Will** of Bertha in the office.

Dr. N. E. Leppo, Duluth, spoke on the "Handicapped Program of the World Health Organization" at a meeting of United Cerebral Palsy of Duluth on September 23.

* * *

At the annual meeting of the American Association of Obstetricians and Gynecologists at Hot Springs, Virginia, in early September, **Dr. L. M. Randall,** chairman of the sections in obstetrics and gynecology at the Mayo Clinic, Rochester, was installed as president of the organization.

* * *

Dr. Walter S. Neff, Virginia, was appointed medical director of the Range Rehabilitation Center in Virginia at a meeting of the governing commission on September 12. The steadily enlarging center now employs two physical therapists, a therapist-aide and a secretary.

* * *

Five consultants have been added to the staff of the Mayo Clinic, Rochester. They are **Dr. Kenneth G. Berge** in the general section, **Dr. Robert J. Gores** in dentistry, **Dr. Stanley Karansky** in anesthesiology, **Dr. William G. Smith** in proctology and **Dr. Jack P. Whisnant** in neurology.

* * *

Dr. Leo G. Rigler, professor in chief of the department of radiology at University Hospitals, has been appointed to the National Advisory Cancer Council by Dr. Leonard A. Scheele, surgeon general of the U. S. Public Health Service.

* * *

GUSTAF A. HEDBERG

Dr. Gustaf Arvid Hedberg, superintendent and medical director of Nopeming Sanatorium, Nopeming, Minnesota, has been awarded the 1955 Dearholt Medal by the Mississippi Valley Conference on Tuberculosis.

The medal, highest honor the organization can bestow, was named after the late Dr. Hoyt E. Dearholt, of Milwaukee, and is presented for outstanding service in tuberculosis control in the Midwest.

The presentation was made by last year's recipient, W. M. Morgan, Alliance, Ohio, October 13, 1955, at the Conference's annual meeting in Des Moines, Iowa.

Dr. Hedberg is a graduate of the University of Minnesota, and was in private practice in that state until 1931, at which time he joined the staff of Nopeming Sanatorium.

He is an assistant professor of medicine, University of Minnesota, Mayo Foundation, and is area consultant in tuberculosis for the Veterans Administration.

Dr. Hedberg holds memberships in the National Tuberculosis Association, American and Mississippi Valley Trudeau Societies, and a number of other professional societies, and has served on the board of directors of the St. Louis County (Minnesota) Tuberculosis and Health Association.

* * *

Dr. Carl Herzog, president of Duke Laboratories of Stamford, Connecticut, has donated $500.00 to the Division of Dermatology, University of Minnesota, in memory of the late Dr. Paul O'Leary of Rochester. The fund is to be used in any manner that Dr. Michelson, the Director, sees fit.

* * *

Dr. Shirley C. Lyons, of New Orleans, Louisiana, president of the Alumni Association of the Mayo Foundation, was the presiding officer of the three-day annual reunion of that organization in Rochester, Minnesota, on October 27, 28 and 29, 1955.

A graduate of Tulane University of Louisiana, Dr. Lyons came to Rochester on May 15, 1921, as a fellow in surgery of the Mayo Foundation, which is a part of the Graduate School of the University of Minnesota.

He took graduate work in general medical and surgical diagnosis, postoperative care, surgical pathology and operative surgery. He was appointed a first assistant in surgery on July 1, 1924.

On November 11, 1924, he returned to the private practice of surgery in New Orleans, where he is now located.

Dr. Lyons was certified in 1939 as a specialist in surgery by the American Board of Surgery, Inc., and from 1930 to 1938 he was assistant professor of surgery in the Louisiana State University Medical Center. In World War II, he served in the U. S. Navy Medical Corps, advancing from the grade of lieutenant commander to that of captain.

Dr. Lyons is a fellow of the American College of Surgeons, and is a member of the American Medical Association, the Southern Medical Association, the Pan American Medical Association, the Alpha Kappa Kappa professional medical fraternity and the Phi Kappa Sigma academic fraternity.

* * *

Dr. and Mrs. Rolf Hovde returned to Winthrop in September after a summer of travel which included several weeks in Europe. While in the Scandinavian countries Dr. Hovde visited several hospitals and attended an international medical meeting in Copenhagen.

* * *

New president of the Minnesota Public Health Conference is **Dr. S. A. Whitson,** Albert Lea. Secretary of the organization is **Dr. Dean S. Fleming,** Minneapolis, director of disease prevention for the state health department.

* * *

Dr. Allyn G. Bridge and **Dr. Roger I. Lienke** are now associated in the practice of pediatrics, with offices at 2908 Lowry Avenue North, Minneapolis.

* * *

Dr. R. Gordon Douglas, chief of the New York Lying-In Hospital, was a house guest of **Dr. and Mrs. William B. Stromme,** Minneapolis, during the week of October 10.

* * *

September was a travel-filled month for **Dr. H. W. Meyerding,** retired staff member of the Mayo Clinic, Rochester. First he attended the annual meeting of the Canadian-American section of the International College of Surgeons in Philadelphia, and as vice president presided over several sessions. He then flew to Miami where he presided as president at the convention of the American Fracture Association. Following that he flew to Havana, Cuba, for a joint meeting of the Cuban Orthopedic Society.

* * *

Principal speaker at a meeting of the Rock Lake Farm Bureau at Balaton on September 27 was **Dr. L. J. Thill,** Balaton, who discussed cardiovascular diseases.

* * *

Dr. T. M. Seery, Austin, attended a refresher course in internal medicine at Duke University, Durham, North Carolina, during the second week of October. The course was sponsored by the American College of Physicians.

* * *

A joint meeting of the Minnesota Industrial Nurses and the Minnesota Academy of Occupational Medicine and Surgery was held at the Leamington Hotel, Minneapolis, on September 28. Principal speakers were **Dr. O. J. Campbell,** Minneapolis, who discussed immediate care of surgical emergencies, and **Dr. John F. Briggs,** St. Paul, who talked on immediate care of medical emergencies.

* * *

Dr. Louis A. Buie, a member of the staff of the Mayo Clinic, Rochester, for thirty-six years, retired on October 1. Dr. Buie organized the section on proctology at the clinic and served as head of it from 1919 to 1953, when he became a senior consultant. He was one of the founders of the American Board of Proctology in 1934. He has written several books on the subject, and many proctologic instruments bear his name. He has always been highly active in both state and national medical affairs.

* * *

Dr. Arnold Lazarow, chairman of the department of anatomy at the University of Minnesota, has been appointed a vice chairman of the Committee of Detection and Education of the American Diabetes Association.

* * *

Dr. E. E. Novak, New Prague, left on September 26 for a vacation trip covering the Pacific Coast, Mexico and Honduras. Making the trip by plane, he planned to visit his daughter in Honduras.

* * *

Dr. Robert B. Pierce has closed his office in Olivia and is now devoting full time to his practice at Renville. For several years he has maintained office hours at both cities.

* * *

Dr. Evelyn E. Hartman and **Dr. Wilford E. Park** were married in Minneapolis on September 23. Dr. Hartman is director of maternal and child health in the Minneapolis Health Department, while Dr. Park is chief of the occupational health service of the department.

* * *

A feature article about **Dr. M. S. Munson,** Barnum, which appeared in the *Duluth News Tribune* on September 4, pointed out the benefits of practicing in a small town. Dr. Munson has practiced at Barnum for six years.

* * *

A three-day surgical symposium was held at the University of Minnesota September 22 to 24 in honor of **Dr. Owen H. Wangensteen,** head of the department of surgery at the university for the last twenty-five years. Sponsor of the event was the Owen H. Wangensteen Surgical Education Foundation, composed of former residents and assistant residents of Dr. Wangensteen at the University Hospitals.

(Continued on Page xl)